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Review Article

Recent update on the management of anaphylaxis

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Anaphylaxis is a life-threatening systemic allergic reaction presenting various clinical manifestations. Its prevalence has increased in almost all age groups and both sexes. Food, venom, and drugs are major causes in both children and adults; a higher prevalence of food-induced anaphylaxis is noted in children, while a higher prevalence of drug-induced anaphylaxis is noted in adults. The pathogenic mechanism is mediated by immunologic and nonimmunologic mechanisms, where mast cells and basophils are key cells that release mediators. A diagnosis of anaphylaxis is mainly based on clinical symptoms and physical findings; however, an increased serum tryptase level is a useful biomarker. Epinephrine is the first-line drug to treat acute symptoms, and an epinephrine auto-injector should be prescribed for each patient. Antihistamines and systemic corticosteroids are used to relieve symptoms. This review updates current issues in the management of anaphylaxis as well as the new guidelines for proper diagnosis and treatment.

Keywords Anaphylaxis; Biomarkers; Diagnosis; Epinephrine; Therapeutics

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Capsule Summary

What is already known

Anaphylaxis is well-known as an acute severe life-threatening hypersensitivity reaction that can occur immediately after exposure to allergens. Epidemiological data on anaphylaxis are still scarce. The International Classification of Diseases-11 system included the definition and code of anaphylaxis which helps clinicians manage anaphylaxis in clinical practice.

What is new in the current study

The anaphylaxis prevalence tends to increase year by year and in almost all age groups. The diagnosis of anaphylaxis is based on clinical vitals and symptoms. Trypsine can help establish the diagnosis, but it has been shown some limitations in recent studies. The World Allergy Organization (2020) suggested a new guideline for diagnosing, treating, and managing anaphylaxis. Our review article updates current issues in epidemiology, treatment, and management of anaphylaxis, especially in Asian populations.

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INTRODUCTION

Anaphylaxis is characterized by acute and severe hypersensitivity reactions that can be life-threatening, even resulting in mortality.[1] According to the International Classification of Diseases-11 systems, the World Health Organization stated that "anaphylaxis is a severe, life-threatening systemic hypersensitivity reaction characterized by a rapid onset of severe symptoms with potentially life-threatening airway, breathing, or circulatory problems, and is commonly associated with skin and mucosal changes".[2] Anaphylaxis has been underrecognized and underdiagnosed because 1) the definitions, diagnosis, and severity grading criteria of anaphylaxis were not agreed among various countries; 2) as most studies had used different sources of data for epidemiological studies using various study methods, it is difficult to estimate the exact morbidity and mortality; 3) there is a lack of anaphylaxis data collected by multiple centers and long-term studies. These limitations caused the delay in epinephrine autoinjector (EAI) prescription for timely usage for patients.[2]

Despite these limitations, anaphylaxis epidemiological parameters (incidence rate, cumulative incidence, point/period/lifetime prevalence, and mortality) have been collected from various sources, including databases from nations, health maintenance organizations, emergency departments (ED), and primary care, have provided approximate data to epidemiologists and clinicians.[3] The findings (on the behalf of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group) based on the major epidemiologic studies in English speaking countries demonstrated that the lifetime prevalence of anaphylaxis ranged from 0.05% to 2.0% (50 to 2,000 episodes per 100,000 persons).[4] Cross sectional randomized digit dial surveys in the adult population of the US showed a higher prevalence of anaphylaxis (1.6% to 5.1%).[5] A recent study reported that anaphylaxis incidence was 32.19 episodes per 100,000 person-years in 2014 in South Korea.[6]

Prevalence and major causative factors are listed in Table 1.[7-13] A systematic review using the estimates of time-trends in hospitalization and mortality showed the increasing prevalence of anaphylaxis in various countries, including Australia, Taiwan, the UK, and the US.[14] Foods were major causes in children, whereas drugs were major ones in adults, which tended to increase with age.[14,15] Case fatality rates (0.5 to 1 case per million) were unchanged or declined in the whole population.[14] Although there have been a few reports on the epidemiology of anaphylaxis in Asian countries, a population-based study using the Korean National Health Insurance database from 2010 to 2014 (based on hospital admission and ED visit) demonstrated a 2-fold increase in the total cases of anaphylaxis and ED visits (20.55 in 2010 vs. 35.33 in 2014, 18.63 in 2010 vs. 31.28 in 2014 and respectively) in all age groups, especially in the adolescent and middle-age groups, compared to the older age groups.[8,16] Regarding causative agents, similar to Western countries, foods (especially hen's egg and cow's milk) were most common in children, whereas drugs (especially nonsteroidal anti-inflammatory drugs [NSAIDs] and antibiotics) were most common in adults in Chinese and Korean populations.[8,16] An adverse drug reaction study in Viet Nam showed a significantly increased prevalence of drug related anaphylaxis (especially antibiotics).[17] There have been few published reports on anaphylaxis-induced mortalities in Asian populations.

The evaluation of anaphylaxis in the primary care systems could be deemed as a difficult problem due to 1) lack of confirmation testing, 2) unavailable standardized testing for all of the antigens and sources, 3) no overall consensus on diagnostic and severity grading criteria.[18] Anaphylaxis diagnosis has been based on the guidelines of the US National Institute of Allergy and Infectious Diseases/Food Allergy, and the Anaphylaxis Network, which were applied to many countries.[7,19] Their diagnosis criteria would cover patients who have cutaneous and gastrointestinal symptoms, acute hypotension and/or known histories of allergen exposure.[18] Previous clinical studies indicated that the application of the guidelines in the diagnosis of anaphylaxis had high sensitivity (from 95.1% to 96.7%), but low specificity (from 70.8% to 82.4%).[20,21] However, high sensitivity of these guidelines is a key factor for assisting physicians with quick diagnosis and identification of patients requiring immediate epinephrine treatment in the ED.[18] With regards to severity grading, a previous study emphasized the strengths and weaknesses of 23 published classification systems, and there has been no consensus on the most appropriate system to grade the severity or its validation.[22] Recently, Korean and German-speaking countries have classified severe anaphylaxis based on Brown's classification systems.[16,19] Additionally, the World Allergy Organization (WAO) has recently suggested an up-to-date grading system,[2] which highlighted the advantages of this system, including classification of systemic reactions, recognition of anaphylaxis/non-anaphylaxis, addition of symptoms (drooling or neurological symptoms), and any available application in the pediatric population.[2]

Hypersensitivity reactions are categorized into four types based on the Coombs and Gell classification: type I, immediate or IgE-mediated response; type II, cytotoxic or IgG/IgM antibody mediated response; type III, immune complex-mediated response; and type IV, delayed or cell-mediated response.[23] The first three types are known as immediate responses because they will occur within 1 hour after exposure, whereas the other is classified as a de-

Table 1. Prevalence of anaphylaxis and causative agents

Country (year)	Method (sample size)	Causative agent	Prevalence of anaphylaxis
South Korea (2020)[7]	Web based survey (n = 558)	Food	Children and adolescents (84.8%): hen's egg (25.4%), cow's milk (18.0%), walnut (9.5%), wheat (8.1%), peanut (4.9%), kiwi (4.2%), pine nut (3.9%), buckwheat (3.2%), soybean (1.8%) Adults (28.3%): shrimp (22.2%), wheat (19.0%), crab (6.3%), soybean (3.2%), peanut (3.2%), beef (3.2%), pork (3.2%)
		Drugs	Children and adolescents (7.2%): analgesics (54.2%), antibiotic (16.7%) Adults (53.8%): antibiotics (50.0%, the most common is cefaclor), analgesics (18.5%), H2 blockers (17.7%), radiocontrast media (1.5%)
		Insect	Children and adolescents (0.3%) Adults (8.1%)
China (2016)[8]	National database (n = 1,952)	Food	Children and adolescents (85.6%): cereal (23.9%), wheat (16.2%), fruit/vegetables (27.2%), tree nuts (4.7%) Adults (74.4%): cereal (47.0%), wheat (43.8%), fruit/vegetables (18.6%), tree nuts (7.9%)
		Drugs	Children and adolescents (2.8%): herb (41.7%), immunotherapy (33.3%), antibiotic (25.0%) Adults (8.6%): herb (36.6%), antibiotic (24.4%), NSAID (17.6%), immunotherapy (9.2%)
		Insect	Children and adolescents (0%) Adults (0.9%)
German-speaking countries (2018)[9]	National database (n = 7,316)	Food	Children and adolescents (60.0%) Adults (16.0%)
		Drugs	Children and adolescents (7.0%) Adults (22.0%)
		Insect	Children and adolescents (22.0%) Adults (52.0%)
US (2019)[10]	National database (n = 462,906)	Food	From 2004 to 2016 for all age groups: incidence increased from 86.3 per 1000 person-years to 239.2 per 1,000 person-years Shellfish-related anaphylaxis: increased from 6.2% to 10.2% Peanut-related anaphylaxis: increased from 22.6% to 34.0%
		Insect	Venom and stings-induced anaphylaxis: fell from 57.0% in 2004 to 38.0% in 2016
European countries (2014)[11]	National database (n = 3,333)	Food	Children (64.9%) Adults (20.2%) Peanut (18.0%), wheat (8.3%), hen's egg (7.8%), cow's milk (7.8%), fruits (7.3%)
		Drugs	Children (4.8%) Adults (22.4%) Penicillin (17.6%), cephalosporines (11.8%), metamizole (10.0%), immunotherapy (10.0%), radiocontrast agent (4.4%)
		Insect	Children and adolescents (20.2%) Adults (48.2%)
Australia (2015)[12]	Hospital admission data	Food	From 2005–2006 to 2011–2012 (fold increase from previous time point) Children: aged 0 to 4 years (increase from 21.7 to 30.3), aged 5 to 14 years (increase from 5.8 to 12.1), aged 15 to 29 years (increase from 6.7 to 10.3) Adults (increase from 3.4 to 4.3)
		Drugs	From 2005–2006 to 2011–2012 (fold increase from previous time point) Children: aged 0 to 4 years (decrease from 0.2 to 0.1), aged 5 to 14 years (increase from 0.6 to 2.4), aged 15 to 29 years (increase from 2.1 to 4.9) Adults (increase from 4.2 to 16.4)
Spain (2015)[13]	Hospital admission data (n = 11,336)	Food	From 1998–2011 (adjusted rates per 100,000 person-years) Foods (19.6%): increase from 0.16 to 0.82 The three most frequently involved foods were milk, eggs, and fish
		Drugs	From 1998–2011 (adjusted rates per 100,000 person-years) Drugs (42.5%): increase from 0.64 to 1.03 Four different classes of drugs (β-lactam antibiotics, NSAIDs, antineoplastic drugs, and diagnostic drugs)

NSAID, nonsteroidal anti-inflammatory drug.

layed response.[23,24] Anaphylaxis belongs to type I hypersensitivity reaction, where mast cells and basophils are key effector cells to release mediators.[23] Recently, contributions of T cells, macrophages, and monocytes have been reported in cases induced by chemotherapy and monoclonal antibodies.[25,26] Therefore, a new classification of anaphylaxis phenotypes is based on type I, cytokine storm like, and mixed reactions.[25,26] Various phenotypes from different pathomechanisms made anaphylaxis difficult to diagnose and treat. This review summarizes recent updates on the diagnosis and management of anaphylaxis.

COMMON TYPES OF ANAPHYLAXIS

Anaphylaxis is one of the mast cell activation disorders induced by various foods (wheat, nuts, eggs, and seafood), drugs (antibiotics, chemotherapies, biologics, radiocontrast media [RCM], and vaccines), and venoms.[2] The profiles of causative agents differ in age, geographical region, and lifestyle. In general, foods are the most common cause of anaphylaxis in children and adolescents, while drugs are the most common causes in adults, followed by foods and insect venom.[7]

Food-induced anaphylaxis

Food-induced anaphylaxis (FIA) is a serious allergic reaction following the ingestion of food allergens, and the incidence of FIA and other types of food allergy continues to rise.[7] The most common causative foods in children and adolescents are eggs, cow's milk, peanuts, wheat, and soybeans.[7,27] Meanwhile, seafood (fish and shellfish) and wheat are the major causes in adults.[28] Allergic response and anaphylaxis to cow's milk have been reported to be 2.0% to 13.0% in children who are able to synthesize IgE antibodies against intruded cow's milk.[29] Egg allergy triggers severe anaphylaxis in infants and children.[30] In addition, peanuts and tree nuts are major causes of anaphylaxis in European children and adolescents, which is related to the presence of asthma comorbidity and increased rate of biphasic reactions.[31] Wheat allergy affects 0.5% to 1.0% of the pediatric population; chronic wheat consumption could lead to anaphylaxis, especially wheat-dependent exercise-induced anaphylaxis.

Risk factors for fatal FIA include comorbidity with asthma, previous history of food allergy, exposure to hidden allergens, and cofactors (exercise, alcohol, and NSAIDs). It is reported that cofactors play a role in 25.6% to 39.0% of anaphylactic reactions in adults and 14.0% to 18.3% in children.[32] Among them, exercise is the major cofactor for FIA, which is called food-dependent exercise-induced anaphylaxis (FDEIA). FDEIA is not very common, but reported up to half of the patients with exercise-induced anaphylaxis (5.0% to 15.0% of all anaphylaxis cases).[33] Shrimp, wheat, soybean, and rice are frequently reported to induce FDEIA, in which shrimp and wheat are most common.[34-36] In some cases of FDEIA, NSAIDs are a cofactor for enhancing anaphylaxis symptoms, especially in patients with wheat-induced FDEIA or plant foods (nuts, seeds, vegetables, and peanut)-derived lipid transfer proteins-induced FDEIA in the Mediterranean area.[37,38] In addition, anaphylactic events can be enhanced by other cofactors, such as temperature change, ingestion of vegetable or meat, food contaminated with aeroallergens (house dust mite and mold), and others (snail, taro, red bean, and mushroom).

Drug-induced anaphylaxis

Drug-induced anaphylaxis is well known as a severe immediate hypersensitivity reaction; however, some drugs are emerging with delayed anaphylactic reactions through other mechanisms. It is caused by numerous drugs, among which antibiotics, NSAIDs, local anesthetics, H_2 blockers, and RCM are common causative drugs, which may be attributed to higher prescription rates. Antibiotics, radiocontrast agents, and intraoperative agents are the common cause associated with mortality.[39] Among antibiotics, cefaclor is most common (account for 50.0%) in Korean adults, followed by NSAIDs, H_2 blockers, and RCM, while anesthetics and chemotherapeutic agents are less commonly reported.[7] Penicillins have been reported as the most prevalent cause in patients with antibiotic-induced anaphylaxis in the US and Vietnam.[17,40] Analgesics, including NSAIDs, are the third most common drug in the US (13.0 per 10,000), followed by opiates (9.8 per 10,000), and local anesthetics (1.4 per 10,000).[40] The prevalence of hypersensitivity and anaphylaxis to RCM differs according to the structures of RCM. RCM is categorized into ionic versus nonionic forms which are further classified into monomer (high osmolality) versus dimeric (low osmolality) forms.[41] Hypersensitivity reaction and anaphylaxis are more common in monomeric ionic forms (3.8% to 12.7% and 0.02% to 0.04% respectively) than in nonionic forms (0.7% to 3.0% for hypersensitivity reactions).[41] Factors for predisposing RCM-induced hypersensitivity reactions include the previous history of RCM hypersensitivity reactions, atopy status, comorbidity with asthma, and severe cardiovascular disease.[42] In another study, RCM-induced anaphylaxis is more common in older patients and with exposure to RCM and iopromide.[43] In addition, perioperative hypersensitivity and anaphylaxis are immediate and potentially life-threatening systemic reactions occurring during the perioperative period. Cardiovascular, respiratory, and integumentary systems are primarily affected by perioperative drugs (which can develop without of skin reactions).[44] Major causative drugs are neuromuscular blocking agents, antibiotics, NSAIDs, anesthetic agents, natural rubber latex, blue dyes, chlorhexidine, and sugammadex (an antidote to aminosteroid muscle relaxants).[45,46]

Venom-induced anaphylaxis

Venom-induced anaphylaxis (VIA) is observed in 1.2% to 3.5% of the general population and is more frequently associated with cardiovascular symptoms.[47] The sensitization and causative venoms can be identified via skin testing or measurement of serum-specific IgE levels to each venom.[47] Approximately 5.0% of patients with VIA exhibit systemic mastocytosis (clonal disorders with an increase in the number of abnormal mast cells in the tis-

sue) that is associated with poor prognosis.[48] Honeybee and vespid venoms are common ones inducing VIA in South Korea.[49]

Vaccine-induced anaphylaxis

Vaccine-induced anaphylaxis is extremely rare. Hypersensitivity can occur because of either vaccine components, such as active agents (inactive or attenuated live vaccine virus and toxoid), additives (antibiotics, preservatives such as gelatin, stabilizers, and adjuvants), or contamination of latex or culture media (ovalbumin from egg white).[50] Lipid components, such as polyethylene glycols (PEG) and polysorbate 80/20 are added to medications as well as vaccines (including coronavirus disease 2019 [COVID-19] vaccine) for improving drug delivery and extending half-life, which could induce anaphylaxis.[50] PEG-induced anaphylaxis mostly occurs from injectable medications with higher molecular weight products such as PEG3350 and PEG4000.[50] In addition, patients with immediate hypersensitivity to PEG3350-containing medications have been reported to exhibit immunological cross-reactivity with polysorbate 80-containing drugs.[51] The risk of anaphylaxis after vaccination has been estimated to be 1.31 (95% confidence interval, 0.90 to 1.84) per million vaccine doses.[52] There are many precautions in patients with severe egg allergy for administering injectable influenza vaccines that contain small amounts of egg protein, and influenza vaccines most frequently induce anaphylaxis.[53,54] Anaphylaxis events are more commonly found in patients with allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, and food/drug allergy, while 41.0% had no history of allergic disease.[53] A recent report demonstrated a higher prevalence of COVID-19 vaccine-associated anaphylaxis (11.1 cases of anaphylaxis per million doses) after a first dose of the Pfizer-BioNTech COVID-19 vaccine regarding the report of the Vaccine Adverse Event Reporting System, among which 71.0% of them occurred within 15 minutes after vaccination.[55] Current mRNA vaccines (Pfizer-BioNTech and Moderna COVID-19 vaccines) contain PEG components such as 2(PEG2000)-N,N-ditetradecylacetamide and PEG2000 dimyristoyl glycerol, respectively, which have been reported as the causes of COVID-19–induced anaphylaxis. Meanwhile, Johnson & Johnson/Janssen COVID-19 vaccine, AstraZeneca severe acute respiratory syndrome coronavirus 2 adenovirus carrier vaccine, and several influenza vaccines (Fluarix quad and Flulaval Quad) contain polysorbate 80.[56,57] Although anaphylaxis after vaccination is rare in all age groups, this immediate-onset and life-threatening condition require adequate medical professionals and supplies to treat potential anaphylactic reactions during vaccination procedures.

DIAGNOSIS

Classification

Anaphylaxis is a severe form of hypersensitivity reactions, which are unpredictable and related to immunological (allergic) and non-allergic reactions. Clinically, hypersensitivity reactions are classified into two types: immediate (arising within 1 hour after exposure) and nonimmediate (delayed reactions arising more than 1 hour after exposure). Immediate reactions can be caused by either mast cells or basophil activation through type I IgE (allergy)/non-IgE (pseudo-allergy) mechanisms or direct complement activation, leading to the release of mediators (histamine and tryptase) to induce variable manifestations, ranging from pruritus to edema, urticaria, and anaphylactic shock. Meanwhile, T cell induced reactions (type IV) and rare events induced by antibodies (type II and III), such as hemolysis, thrombocytopenia, damaged vascular walls, and glomeruli, have been reported related to delayed reactions.[24]

Severity grading

Although grading systems for the severity of anaphylaxis have several limitations, Table 2[19,47,58-60] summarizes recent studies which have investigated demographic, clinical characteristics, and biomarkers for the severity of anaphylaxis according to each caus-

Table 2. Severity-related factors for anaphylaxis

Factor	Child	Adult
Advanced age[47,58]	Milder reactions for VIA	Higher risk in adults (age around > 40 years) for VIA
Bronchial asthma[19]	√	√
The symptoms began less than 5 minutes after the allergen exposure[59]	√	-
Severe cardiovascular disease[19]	√	√
Drugs (promote mast cell activation, leukotriene secretion such as NSAIDs)[19]	√	√
Elevated baseline tryptase levels[47]	√	√
Hereditary α-tryptasemia[60]	Cases of VIA and idiopathic anaphylaxis	Cases of VIA and idiopathic anaphylaxis
Mastocytosis[60]	√	Cases of VIA

VIA, venom-induced anaphylaxis; NSAID, nonsteroidal anti-inflammatory drug.

ative agent. Six significant risk factors for severe anaphylaxis in Hymenoptera venom allergy include short interval from sting to reaction, absence of urticaria or angioedema during anaphylaxis, older age, male sex, elevation in baseline serum tryptase level, and diagnosis of systemic mastocytosis.[47,58] In addition, hereditary α-tryptasemia (excess copies of α-tryptase at *TPSAB1*) is associated with increased serum tryptase levels and severe anaphylaxis in patients with systemic mastocytosis, VIA, and idiopathic anaphylaxis, in which patients with hereditary α-tryptasemia show 500-fold higher serum tryptase level than the general population.[60,61] Moreover, risk factors for severe anaphylaxis have been reported to be advanced age, severe cardiovascular disease, bronchial asthma, systemic mastocytosis, and use of certain drugs, such as NSAIDs, which promote mast cell activation or leukotriene secretion.[19] A multicenter prospective observational study showed that asthma history, symptom onset within 5 minutes after allergen exposure, unhealthy appearance, tachycardia, and hypotension are independent risk factors for severe anaphylaxis in children.[59]

Clinical features and predisposing factors

Clinical manifestations at the time of presentation are helpful in the diagnosis of anaphylaxis.[2] Diagnostic criteria based on the guideline suggested by WAO in 2020 are 1) sudden onset of an illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue, or both (generalized hives, pruritus or flushing, and swollen lips-tongue-uvula) plus at least one of the following: respiratory compromise (dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, and hypoxemia) reduced blood pressure or symptoms of end-organ dysfunction; and 2) acute onset of hypotension or bronchospasm, or laryngeal involvement after exposure to a known or probable allergen (minutes to several hours), even in the absence of typical skin involvement (urticarial rash/erythema/flushing, and angioedema).[2] Moreover, laboratory tests can help physicians evaluate anaphylaxis phenotypes and find causative agents. As shown in Table 3,[25,26,62-66] inflammatory mediators (histamine, tryptase, chymase, carboxypeptidase A3, and platelet-activating factor) are measured during the acute phase and/or stable condition (at least 24 hours after all signs and symptoms have been resolved) to confirm the diagnosis of anaphylaxis.[67] Meanwhile, the basophil activation test, serum-specific IgE measurement, and skin tests as well as component-resolved diagnostics are used to find causative agents.

Potential biomarkers

Histamine and tryptase are the most common inflammatory mediators derived from activated mast cells/basophils. Although histamine exhibits important biological reactivities, such as vasodi-

Table 3. Biomarkers for anaphylaxis

Biomarker	Secreted source	Advantage	Disadvantage
Serum/plasma/urine histamine[62]	Mast cells Basophils	Histamine can be useful for the evaluation of early-onset anaphylaxis	Insufficiency for evaluating anaphylaxis
Serum tryptase[25,26]	Mast cells Basophils	High specificity and more stable than histamines The gold standard for anaphylaxis diagnosis	Low sensitivity Increases in some cases of adult healthy controls Limitations in food-allergy in children
Skin tests[25,26]	-	Useful for evaluation of penicillin allergy, food allergy A safe and non-invasive method for patients with a history of anaphylaxis and mastocytosis	False positives: β-blockers and angiotensin-converting enzyme inhibitors False negatives: Hymenoptera hypersensitivity Monoclonal antibody: the specificity and sensitivity are not well-defined.
Specific serum IgE[25,26]	B cells	High sensitivity and specificity in Hymenoptera venom-specific IgE Evaluation of platins-specific IgE in the short-time Evaluation of cross-reactivity with drugs	Limitations in food allergies, penicillin allergy
Component-resolved diagnostics[63-65]	-	Prediction of allergic reaction severity Have greater specificity in food allergy Capable of detecting the causal agent A useful tool in Hymenoptera allergy	Lower sensitivity in food allergy Expensive, labour intense
Basophil activation test[25,26,66]	Basophils	Easily assessed Useful diagnosis and management for β-lactams, muscle relaxants, Hymenoptera venom allergies, fish allergy A true reflection of sensitized mast cells	Expensive, labour intense
Others[25,26]	Serum PAF, serum TNF-α, IL-6, and IL-1β, Prostaglandin D2 and leukotrienes E4 and C4, chymase and carboxypeptidase, mast cell activation test		

PAF, platelet-activating factor; TNF-α, tumour necrosis factor α; IL, interleukin.

lation and smooth muscle contraction, its half-life in plasma or serum is too short to be measured in the ED after anaphylaxis occurs. Therefore, levels of histamine and its metabolite methylhistamine are more frequently detected in urine than in plasma or serum, particularly urine collected for over 24 hours which supports the diagnosis of mast cell activation syndromes, including systemic mastocytosis and secondary disorders with Ig-E-mediated disorders, anaphylaxis, and autoimmune disorders.[68] Tryptase is the major enzyme stored within human mast cells. Tryptase levels are measured by the immunoCAP system in serum samples. It is more useful to measure at 2-time points; acute (sampled between 30 minutes and 2 hours after symptom initiation) and baseline tryptase levels (sampled before the event or at least 24 hours after all signs and symptoms have resolved).[67] Baseline tryptase levels are considered low if they are lower than 11.4 ng/mL. Mast cell degradation during anaphylactic events is considered if acute levels increase higher than 2 ng/mL plus 1.2 times from baseline.[67] To date, serum tryptase has been documented to be the most useful biomarker for the diagnosis of anaphylaxis, although there have been some reported cases of anaphylaxis showing normal serum tryptase levels.[69] Other mediators of inflammation, such as arachidonic acid-derivated proinflammatory mediators (prostaglandin D_2 and cysteinyl leukotriene E_4), tumour necrosis factor α, interleukin 6, and interleukin 1β levels, are derived from T cells, neutrophils, eosinophils, and endothelial cells through non-IgE mechanisms, which can be increased in serum samples in patients with anaphylaxis, albeit they are not useful in clinical practice.[70]

Identification of causative and exacerbating factors

Culprit allergens can be identified by a careful history. Skin tests, allergen-specific IgE measurement, and component-resolved diagnostics can be used to find causative agents and severity. Skin tests are considered safe for patients with a history of anaphylaxis and applied to identify sensitization to numerous allergens, including airborne, food allergens, drugs (β-lactam, general anesthetics), and Hymenoptera venom triggers. They have some limitations to the diagnosis of patients with anaphylaxis induced by cross-reactivity or hidden allergens. Component-resolved diagnostics may overcome these limitations through their ability to identifying some molecules present in allergenic extracts.[71,72] Additionally, *ex vivo*, basophil activation tests are used to diagnose IgE or non-mediated reactions using sensitized basophils from each patient. It is useful for evaluating immediate reactions to β-lactam antibiotics and muscle relaxants as well as FIA.[73,74] It is ideal to perform these tests 4 weeks after the acute episode.[2] Allergists and immunologists should educate patients about causative agents and related cross-reactivities for active avoidance.[2] In addition, exposure to other risk cofactors should be avoided to reduce recurrence.

ACUTE MANAGEMENT

Anaphylaxis is a life-threatening disease that occurs immediately after exposure to allergens. Acute management should be rapidly initiated to decrease the high risk of death.[2] First-line treatment options include epinephrine administration, airway protection, and circulation support.[75] Epinephrine injection is the most important modality for acute treatment.[25] Second-line drugs (antihistamines, inhaled β-2 adrenergic agonists, and corticosteroids) play roles as supportive therapeutics to reduce symptoms, but they cannot replace epinephrine as a first-line treatment.[76]

Epinephrine

Epinephrine regulates cardiovascular and respiratory systems via improving vasoconstriction, peripheral vascular resistance, bronchoconstriction, and mucosal edema.[19,25] Epinephrine treatment should be immediately given after removing triggers and assessing current patient conditions according to emergency protocols.[2,19] According to the WAO guideline, the recommended injection dose is between 0.01 mg/kg of body weight and up to a maximum total dose of 0.5 mg (equivalent to 0.5 and 1 mg/mL [1:1,000], respectively). For instance, infants weighing under 10 kg are given a dose of 0.01 mg/kg of 1 mg/mL (1:1,000) epinephrine, children aged 1 to 5 years 0.15 mg, children aged 6 to 12 years 0.3 mg, and teenagers/adults 0.5 mg.[2] Intramuscular administration to the vastus lateralis of the quadriceps, instead of subcutaneous or intravenous administration, is recommended because of its effective and rapid absorption.[2,77] Additionally, the requirement of more than 1 dose of epinephrine every 5 to 15 minutes should be considered in patients who present with 1) poor response to a first dose, 2) history of more than 1 dose administrations of epinephrine due to anaphylaxis or biphasic anaphylaxis, refractoriness to treatment, food allergy, severe asthma, or current medications such as β-blockers.[19] After the initial management, patients should lie down with their lower limbs elevated or in their most comfortable position. Patients with anaphylaxis should be immediately transported to the hospital. Comprehensive care and quick assessment of patients is necessary even in the ambulance. After arriving at hospital, vital signs, such as electrocardiogram, pulse, and blood pressure should be monitored in order to evaluate degree of severity, shock, and the risk of biphasic reactions.[19,78] High-flow oxygen (100.0%) should also be given to all patients with cardiovascular or pulmonary reactions.[25]

Antihistamines

Antihistamines are beneficial for relieving cutaneous manifestations and rhinoconjunctivitis.[19,79] First-generation H_1-antagonists (dimetindene and clemastine) could relieve cutaneous symptoms, and be available for intravenous injection, but are limited by their side effects such as sedation, confusion, antimuscarinic effects (tachycardia, mouth dryness, etc.), and hypotension.[79,80] As second-generation H_1-antagonists have no parenteral forms, they cannot be used in the acute management of anphlaxis.[2,76]

Glucocorticosteroids

Glucocorticosteroids are well-known as secondary drugs for preventing biphasic reactions.[2,19] However, recent Cochrane reviews evaluated the benefits and harms of glucocorticoid treatment in acute management, and found no clear evidence for the use of glucocorticoids in anaphylaxis treatment in the ED or for biphasic reaction prevention.[81,82] High doses of glucocorticoids (500–1,000 mg in adults) can be prescribed for patients with generalized urticaria, concomitant asthma, airway edema, or stridor after being stabilized.[19,83] In cases of children, prednisolone in the form of suppositories or enemas (a dose of 2 mg/kg) as well as in an injectable form is suitable for administration.

Glucagon and inhaled β–2 adrenergic agonists

Parenteral treatments of glucagon have supportive effects in patients with poor response to epinephrine or in those using β-blockers.[84] Inhaled β-2 adrenergic agonists are given in patients with bronchoconstriction.[2]

Special issues in the acute management

Clinicians should be careful to administer epinephrine in some patients. First, unavoidable adverse effects- and overdose-caused symptoms, including transient anxiety, headache, dizziness, palpitations, etc., are noted.[18,76] Secondly, if patients do not respond to intramuscular epinephrine injections, they can receive an intravenous infusion of epinephrine by trained health care professionals under intensive monitoring instead of the third dose of epinephrine.[76,85-87] Thirdly, patients with a history of cardiovascular diseases should be carefully managed because epinephrine has arrhythmogenic effects and increases cardiac output.[88]

Infants need to be carefully monitored.[76] There are some difficulties in evaluating this age group because 1) they are unable to describe their symptoms; 2) there are no specific criteria for this population; and 3) overdose epinephrine treatment which may induce life-threatening symptoms (pulmonary edema) could be masked by anaphylaxis symptoms.[76,89] Recent studies have shown higher frequencies of initial antihistamine treatment (more than 80%), followed by intravenous fluid and systemic steroid treatment instead of initial intravascular epinephrine treatment in the ED in South Korea.[7,90,91] However, the benefits of these drugs in the infant population have not yet been evaluated in large-scale and randomized controlled studies.

CHRONIC MANAGEMENT

After acute treatment, stabilized patients should be given long-term management by specialists. In addition, causative agents and exacerbating factors to prevent recurrent anaphylaxis and an EAI should be prescribed with education about emergency use.[76,83]

EAI

The prescription rate is relatively low, although it has been increasing from 2.4% in 2010 to 6.9% in 2014.[7] Commercial EAIs containing 4 doses (0.1, 0.15, 0.3, and 0.5 mg).[2] A dose of 0.15 mg is recommended for patients weighing 15 to 30 kg, whereas a dose of 0.3 mg is recommended for patients weighing 30 kg or more.[92] EAIs with 0.1 mg (suitable for patients weighing less than 15 kg) and 0.5 mg (suitable for patients weighing more than 50 kg) are not commercially available in the majority of countries, including Korea.[7] There are some issues regarding the depth of drug delivery in children. A recent study using ultrasound evaluated needle length and propulsive force from skin to bone in 100 children weighing less than 15 kg with food allergies. A dose of 0.15 mg was reported to have the risk of injection into the bone in such subjects.[93] In patients with a bodyweight of more than 40 kg who receive an EAI at a dose of 0.3 mg, the needle may ne too short to correctly deliver epinephrine to the appropriate intramuscular structures when evaluated by ultrasound,[92] with only 77.0% of the dose absorbed.[93] In these patients, use of 0.5 mg EAI should be considered.

The prescription of EAI (at least 1 dose) is recommended by the European Academy of Allergy and Clinical Immunology in patients with history of food, latex, and aeroallergen-induced anaphylaxis, exercise-induced anaphylaxis, idiopathic anaphylaxis, uncontrolled severe asthma with food allergy, systemic cutaneous reactions with venom allergy in adults and children, and mast cell disorders.[83] In some countries where EAIs are not available, prefilled epinephrine syringes can be used. However, there is insufficient evidence to prove that this prefilled syringe (1 mg/mL epinephrine) is stable and sterile.[94]

Allergen immunotherapy and drug desensitization

Immunomodulatory approaches should be considered in venom

immunotherapy and drug desensitization.[83] Indeed, patients with VIA show the best response to subcutaneous venom immunotherapy for preventing anaphylaxis in both children and adults.[78,83] For drug desensitization, administration of drugs (with increasing doses) can achieve a tolerant state to targeted drug doses.[83] Desensitizations can be successful for patients with anaphylaxis induced by chemotherapy, biologics, NSAIDs, and antibiotics.[26]

Omalizumab

Omalizumab, an anti-IgE antibody, down-regulates the expressions of high-affinity IgE receptor andFcεRI on the surfaces of basophils, mast cells, and dendritic cells, suppressing the IgE-dependent cascade.[75] Omalizumab has been applied to manage patients with moderate to severe asthma and/or those with chronic inducible and spontaneous urticaria.[95] Recently, it has been applied to manage severe food allergy, eosinophil-related gastroenteritis, acute reactions after rush immunotherapy, and mast cell disorders even in idiopathic anaphylaxis, although further randomized and controlled trials are needed.[96-99]

CONCLUSION

Anaphylaxis is a severe life-threatening systemic hypersensitivity reaction in all age groups with increasing prevalence, ED visits, and hospitalization rates. Food allergens and drugs are major causes of anaphylaxis among children and adults. The diagnosis is based on clinical symptoms and signs. An increased acute serum tryptase level is a useful biomarker for the diagnosis of anaphylaxis. Skin testing, serum-specific IgE (measurement including components), and basophil activation tests are used to identify causative agents. Epinephrine should be administered for acute management of anaphylaxis. For chronic management, proper treatment with avoidance of causative factors is essential to prevent recurrent anaphylaxis. EAI shoud be given to patients with high risk factors. Infants and old patients should receive specific treatment and monitoring.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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