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Recent Insights into the Epidemiology and Management of Anaphylaxis

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Anaphylaxis is a severe, rapidly developing systemic hypersensitivity reaction that can be life-threatening if not promptly identified and treated. Its global incidence is on the rise, especially among children, though fatal outcomes remain uncommon. This review summarizes the current understanding of anaphylaxis, covering its epidemiology, triggers, acute management, and strategies for long-term prevention, with emphasis on cases caused by food, medications, and insect stings.

The estimated lifetime prevalence of anaphylaxis ranges from 0.05% to 2%. In children, food is the primary trigger, whereas in adults, medications are the most commonly responsible. The main culprits for food-related anaphylaxis differ by region: in Western countries, peanuts and tree nuts predominate; in East Asia, hen's eggs and cow's milk are most frequent; and in Southeast Asia, seafood is the leading cause. Drug-induced anaphylaxis-often the main cause of anaphylaxis-related deaths worldwide-is increasing due to the growing use of chemotherapies and biologic agents. Insect stings cause about 10% of all cases and remain the most common cause of fatal anaphylaxis.

Intramuscular adrenaline continues to be the primary treatment, yet its administration is often delayed or insufficiently used. Patients should be prescribed adrenaline autoinjectors following an initial reaction, but availability and usage rates differ widely across countries. Education for patients and caregivers and the creation of clear action plans are essential. New alternatives, such as intranasal and sublingual adrenaline devices, are being developed to improve access and minimize hesitation in treatment.

For prevention, VIT is well established and highly effective, preventing systemic reactions in over 90% of cases. Drug desensitization enables safe administration of necessary medications despite confirmed allergies, and this approach is suitable for all ages, including children. Oral immunotherapy for food allergens can increase tolerance levels and lower the chance of accidental exposure in selected patients, though safety concerns limit its widespread use.

Biologic therapies like omalizumab present new treatment avenues for patients with multiple food or drug allergies. Recent studies have shown that omalizumab can raise the threshold for reactions to peanuts and other allergens in children. Case reports also indicate it may improve safety during drug desensitization, including for chemotherapy.

Ongoing progress in diagnosis, emergency readiness, immunotherapies, and biologics continue to broaden the range of options for managing anaphylaxis. Nonetheless, gaps in access, awareness, and supporting evidence-particularly for children and older adults-underscore the need for additional research and health system investment.

INTRODUCTION

Anaphylaxis represents one of the most severe and potentially life-threatening outcomes of allergic conditions. It is marked by a rapid-onset systemic hypersensitivity reaction (HSR) that can involve multiple organ systems at the same time. The World Allergy Organization (WAO) anaphylaxis committee defines anaphylaxis as follows:

"Anaphylaxis is a serious systemic HSR that is usually rapid in onset and may cause death. Severe anaphylaxis is characterized by potentially life-threatening compromise in the airway, breathing, and/or circulation, and may occur without typical skin features or circulatory shock being present".[1]

According to this definition, anaphylaxis is considered highly probable when at least one of two criteria occurs within minutes to hours after exposure (Table 1).[1] The foundation of anaphylaxis management remains early recognition and immediate action, with intramuscular adrenaline firmly established as the first-line treatment. Despite considerable progress in understanding its causes and treatment options, anaphylaxis continues to pose major challenges for healthcare providers around the world. This review seeks to present current epidemiological patterns and evidence-based recommendations for both the acute management and long-term prevention of this potentially fatal condition.

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TRENDS IN ANAPHYLAXIS EPIDEMIOLOGY

Prevalence

Recent estimates indicate that the lifetime prevalence of anaphylaxis in the general population ranges from about 0.05% to 2%.[1] Based on emergency department records, the annual incidence is thought to fall between 50 and 112 cases per 100,000 people.[2] However, these numbers differ widely among countries and regions due to variations in reporting standards, study groups, and how national health data are coded.

In developed nations, the prevalence of anaphylaxis has risen over the past 20 years. A notable rise has been seen in hospital admissions for food-induced anaphylaxis among children.[3] For example, data from New Zealand show a 2.8-fold increase in food-related anaphylaxis between 2006 and 2015.[4] Likewise, research in Singapore found that childhood anaphylaxis cases have doubled in recent years.[5] On the other hand, data on fatal anaphylaxis are still scarce. The estimated fatality rate is about 0.5-1 case per million people each year and has been declining in many parts of the world.[6] Even with a rising prevalence, deaths from food-induced anaphylaxis have decreased over time.

Drug allergies have also become more common globally, now affecting over 7% of the population.[7] In several countries, medications have become the leading cause of fatal anaphylaxis, and deaths due to drug-induced reactions continue to rise-unlike the trends observed for food-induced cases.[8]

Insect sting-induced anaphylaxis, often caused by wasp or ant stings, makes up roughly 10% of all cases.[7] Although reports vary, insect stings remain an important cause of severe reactions and are the second most frequent cause of anaphylaxis-related deaths, following drug-induced cases.[8]

TRIGGERS

Food

The triggers for food-induced anaphylaxis differ greatly depending on region, age group, and local dietary habits. Recognizing these variations is essential for creating effective region-specific prevention measures and clinical management guidelines.

Among children and adolescents (Table 2), research from the United States (US) and Europe consistently identifies peanuts and tree nuts as the main causes of anaphylactic reactions.[9-11] A national survey in France similarly found that peanuts and tree nuts were the most common foods linked to pediatric anaphylaxis.[12] However, significant differences can be seen within Europe itself. For example, a study conducted in Spain reported that cow's milk caused more cases of anaphylaxis than peanuts, indicating that local dietary customs and the timing of food introduction may affect which triggers are most common.[13] Although data from the Middle East are still limited, findings from Israel show that tree nuts are the leading trigger, followed by cow's milk and peanuts.[14] These results partly match European trends but also reveal distinct regional eating patterns. More studies in Asia have shown these unique trends clearly. In Japan and Korea, hen's eggs and cow's milk are more frequent triggers than tree nuts, which is different from the pattern seen in Western countries.[15,16] By contrast, in coastal areas such as Hong Kong, Singapore, and Thailand, crustaceans are the main triggers reported for food-induced anaphylaxis, which likely reflects the high levels of seafood consumption in these places.[17-19] To better understand these regional patterns, the Asia-Pacific Research Network for Anaphylaxis has set up a prospective pediatric anaphylaxis registry covering Thailand, Singapore, Hong Kong, and Qingdao. Between 2019 and 2022, 721 episodes were documented in 689 patients across 16 participating centers.[20] Food was identified as the primary trigger, but the specific allergens varied by country: eggs and cow's milk were common triggers among children under 3 years old; nuts were the most frequent in Hong Kong and

TABLE 1. Definition of Anaphylaxis.[1]

Anaphylaxis is highly likely when any one of the following 2 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 onset 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.

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 þ [2 x 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).
World allergy organization anaphylaxis guidance 2020 Carrdona et al. World Allergy Organ J. 2020;10:100472.

Singapore; wheat was the top allergen in Bangkok; and shellfish-induced anaphylaxis became more common with increasing age. Australia shows a pattern similar to that of the US, where peanuts and tree nuts are the leading causes of anaphylaxis in children and adolescents.[21] These regional patterns underscore the need to take local dietary customs, allergen exposure, and cultural habits into account when interpreting anaphylaxis trends and developing public health measures.

Reports on food-induced anaphylaxis among adults and older adults show different trends compared to children (Table 3). In the US, two large cohort studies found that crustaceans and fish are the main triggers for adults, followed by peanuts and tree nuts.[10,22] In Europe, data from the European Anaphylaxis Registry identified wheat, crustaceans, and hazelnuts as the most frequent food triggers among adults and older adults.[23] Likewise, a national survey in France reported crustaceans, peanuts, and tree nuts as common causes, highlighting the ongoing significance of shellfish and nut allergies in Western adult populations.[12] In Asia, patterns differ again. In Japan, wheat and buckwheat are the two most common foods responsible for adult anaphylaxis, reflecting distinctive dietary staples.[24] In contrast, crustaceans have consistently been reported as the main cause in Korea, Singapore, and Thailand.[16,18,19] High seafood consumption in these countries likely explains this trend. In Oceania, especially in New Zealand, crustaceans and fish are the most frequent triggers, followed by peanuts and tree nuts.[25] These

TABLE 2. Recent Epidemology of Food-Induced Anaphylaxis in Children and Adolescents.

Country	Cases (n)	Causative antigen			Author
		1st	2nd	3rd	
US	7,310	Peanut (32%)	Tree nuts (20%)	Cow's milk (6%)	Motosue et al.[9]
US	2,043	Peanut (27%)	Tree nuts (11%)	Fish (7%)	Poirot et al.[10]
Europe	1,291	Peanut (25%)	Tree nuts (22%)	Hen's egg (10%)	Grabenhenrich et al.[11]
France	82	Peanut/Tree nuts (35%)	Cow's milk (11%)	Hen's egg (7%)	Corriger et al.[12]
Spain	106	Cow's milk (42%)	Hen's egg (24%)	Peanut (17%)	Alvarez-Perea et al.[13]
Israel	317	Tree nuts (28%)	Cow's milk (24%)	Peanut (8%)	Cohen et al.[14]
Japan	1,948	Hen's egg (19%)	Cow's milk (17%)	Tree nuts (11%)	Kitamura et al.[15]
Korea	284	Hen's egg (25%)	Cow's milk (18%)	Tree nuts (13%)	Jeong et al.[16]
Hong Kong	133	Crustaceans (19%)	Fish (17%)	Tree nuts (14%)	Li et al.[17]
Singapore	137	Crustaceans (17%)	Peanut (10%)	Tree nuts (7%) Cow's milk (7%)	Goh et al.[18]
Thailand	38	Crustaceans (53%)	Fish (11%)	Mollusks (5%)	Rangkakulnuwat et al.[19]
Australia	53	Peanut (34%)	Tree nuts (23%)	Cow's milk (8%) Crustaceans/fish (8%)	McWilliam et al.[21]

US, United States.

TABLE 3. Recent Epidemiology of Food-Induced Anaphylaxis in Adults.

Region	Cases (n)	Causative antigen			Author
		1st	2nd	3rd	
US	90	Crustaceans (34%)	Tree nuts (20%)	Peanuts (12%)	Gonzalez-Estrada et al.[22]
US	1,970	Fish (20%)	Peanuts (13%)	Tree nuts (10%)	Poirot et al.[10]
Europe	1,254	Wheat (14%)	Crustaceans (10%)	Hazelnut (7%)	Aurich et al.[23]
France	55	Crustaceans (31%)	Peanut/Tree nuts (16%)	Hen's egg (2%)	Corriger et al.[12]
Japan	3,587	Wheat (5%)	Buckwheat (3%)	Peanut (1%)	Muramatsu et al.[24]
Korea	63	Crustaceans (30%)	Wheat (19%)	Fruits (5%)	Jeong et al.[16]
Singapore	99	Crustaceans (32%)	Peanut (4%)	Mollusks (2%) Wheat (2%)	Goh et al.[18]
Thailand	171	Crustaceans (49%)	Fish (8%)	Mollusks (5%)	Rangkakulnuwat et al.[19]
New Zealand	1,598	Crustaceans/fish (7%)	Peanuts/Tree nuts (6%)	Hen's egg/cow's milk (1%)	Kool et al.[25]

US, United States.

TABLE 4. Epidemiology of Drug-Induced Anaphylaxis in Various Regions.

Region	Data source	Study period	Cases (n)	Causative antigen			Author
				1st	2nd	3rd	
Worldwide	FDA Adverse Event Reporting System (FAERS)	1999-2019	47,490	Antibiotics (14.9%)	Monoclonal antibodies (13.1%)	Analgesics (8.8%)	Yu et al.[38]
Europe	European Anaphylaxis Registry (EAR)	2007-2019	1,815	Analgesics (41.3%)	Antibiotics (33.2%)	Local anesthetics (7.4%)	Hanschmann et al.[39]
US	FDA Adverse Event Reporting System (FAERS)	1999-2019	13,899	Monoclonal antibodies (20.4%)	Antibiotics (10.2%)	Analgesics (6.6%)	Yu et al.[38]
Latin America and Spain	An online questionnaire designed by the Anaphylaxis Interest Group of the SLAAI for this project	2018-2021	332	NSAIDs (41.9%)	Antibiotics (35.5%)	Anesthetics (3.3%)	Jares et al.[40]
Japan	The anaphylaxis registry of training and teaching facilities certified	2015-2017	89	Contrast agent (33%)	Antibiotics (16%)	NSAIDs (16%)	Sato et al.[32]
China	The Beijing Pharmacovigilance Database	2004-2014	1,189	Antibiotics (39.3%)	Traditional Chinese medicine (11.9%)	Contrast agent (11.9%)	Zhao et al.[41]
Korea	Multicenter web-based registry	2016-2018	154	Antibiotics (44.8%)	Analgesics (24.0%)	H_2 blocker (14.9%)	Jeong et al.[16]

US, United States; FDA, Food and Drug Administration; SLAAI, Sociedad Latinoamericana de Alergia, Asma e Inmunología

international findings emphasize the major role of regional eating habits in allergen exposure and sensitization among adults and highlight the importance of region-specific strategies for managing food-induced anaphylaxis.

A comparison of food-induced anaphylaxis in children and adults reveals clear differences in the foods responsible. In children, peanuts, tree nuts, hen's eggs, and cow's milk are the main triggers, which reflects early exposure and sensitization during childhood. In adults, however, anaphylaxis is more often caused by seafood-especially crustaceans and fish-as well as wheat and, in certain regions, buckwheat.

Since Maulitz et al.[26] first described food-dependent exercise-induced anaphylaxis (FDEIA) in 1979, its incidence appears to have been increasing. Aihara et al.[27] later reported that the prevalence of FDEIA among Japanese junior high school students was 0.017%. More recent studies from different countries have found that wheat, crustaceans, and fruits are the most common foods linked to FDEIA.[28-32] Provocation tests have also confirmed that wheat is the leading trigger, followed by crustaceans and fruits.[33]

Several factors help explain the differences in food-induced anaphylaxis patterns between children and adults. Many food allergies common in childhood-such as those to cow's milk and hen's eggs-often resolve with age, which makes them less common in adults. In contrast, adults may develop new sensitizations to seafood and wheat due to greater exposure through diet, certain workplaces, or other external influences. Regional eating habits also have a strong impact, as seen in the high rates of buckwheat allergy in Japan and seafood allergies in coastal areas of Asia.

Pollen-food allergy syndrome (PFAS) is another important factor in food-induced anaphylaxis. Although PFAS usually causes mild symptoms limited to the mouth and throat, it can sometimes lead to severe systemic reactions, including anaphylaxis. Recent studies have identified the gibberellin-regulated protein Pru p 7, which cross-reacts with pollens from Japanese cedar (*Cryptomeria japonica*) and cypress (*Chamaecyparis obtusa*).[34-36] In Central Europe, Pru p 3-a lipid transfer protein in peaches-has been associated with systemic reactions and is recognized as an important cause of food-induced anaphylaxis in that region.[37] Unlike many other PFAS-related proteins that are usually inactivated by cooking, gibberellin-regulated proteins and lipid transfer proteins are highly resistant to heat and digestion and can trigger severe systemic reactions, including anaphylaxis.

Drugs

A wide range of agents can cause drug-induced anaphylaxis. Antibiotics and pain relievers are the most commonly reported triggers, followed by chemotherapy drugs, radiocontrast agents, and medications used during surgery. The specific drugs involved vary by region and according to how data are collected.[16,32,38-41] Table 4 provides a summary of epidemiological findings from various countries.

Globally, antibiotics are the main cause of drug allergies and fatal drug-induced anaphylaxis.[8,16,38,41] Among these, ß-lactam antibiotics-such as penicillin and cefazolin-are the most frequent triggers, with quinolones and other antibiotic classes following.[38] Accurate diagnosis and careful selection of alternative treatments are crucial for managing antibiotic allergies, and it is important to note that not all penicillins and cephalosporins cross-react.[42] Anaphylaxis related to pain relievers is especially common in Europe.[39] Hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) is divided into two main types: nonselective reactions caused by cyclooxygenase-1 inhibition and selective IgE-mediated allergic reactions.[41] The latter is responsible for IgE-mediated drug-induced anaphylaxis, often involving pyrazolones, diclofenac, ibuprofen, and, outside of NSAIDs, paracetamol (acetaminophen).[39,43] Radiocontrast agents, especially iodine-based contrast media, are another major cause of anaphylaxis and can sometimes lead to fatal reactions.[7] Although gadolinium-based agents are generally considered safer, anaphylaxis has still been reported.[44] Immediate reactions to contrast media are typically not IgE-mediated but are thought to involve direct mast cell activation or activation of the complement system.[45] In Japan, radiocontrast agents are among the most common causes of drug-induced anaphylaxis.[46] For chemotherapy drugs, platinum-based agents, taxanes, doxorubicin, asparaginase, and epipodophyllotoxins are the drugs most often linked to anaphylactic reactions.[47,48] A single-center study conducted in Korea also found that chemotherapy drugs were the leading cause of drug-induced anaphylaxis.[49] In recent years, monoclonal antibodies have become notable triggers of anaphylaxis, especially in North America, where they now rank as the second most common cause of drug-induced anaphylaxis.[38] HSRs to monoclonal antibodies are diverse and can involve IgE-mediated processes, cytokine release reactions, and IgG-mediated mechanisms, with clinical features differing depending on the specific drug.[50] As the use of monoclonal antibodies continues to grow, the global incidence of anaphylaxis linked to these therapies is likely to increase. Moreover, certain components in medications, such as alpha-gal and polyethylene glycol, have also been identified as causes of anaphylaxis.[51,52] Recent research has further shown that some drugs-particularly neuromuscular blocking agents, opioids, and antibiotics like fluoroquinolones-can trigger anaphylaxis-like reactions by directly activating mast cells through the mast cell-related G protein-coupled receptor X2 pathway.[53,54]

Insect stings

The types of insects that cause severe immediate allergic reactions differ by region; however, the majority of systemic allergic responses to insect stings are caused by insects belonging to the order Hymenoptera.[55] Clinically significant Hymenoptera are categorized into four groups: *Vespinae, Polistinae, Apidae*, and *Formicidae*, with ants also classified under Hymenoptera (Table 5).

The Vespidae family, which includes Vespinae and Polistinae, is the most common source of systemic reactions to insect stings.[55] The Vespinae group includes genera such as *Vespula* (yellow jackets), *Vespa*, and *Dolichovespula* (hornets). *Vespula* species are widely distributed across the temperate regions of Europe, North America, and Asia. In Europe, *Vespula* is the most frequent cause of insect sting-induced anaphylaxis, accounting for about 70% of cases.[56] *Vespa velutina*, originally native to Southeast Asia, has recently spread throughout Europe and is now the primary cause of insect sting-related anaphylaxis in Spain.[57]

Polistinae (paper wasps) are significant causes of anaphylaxis. In Japan, *Polistinae* account for 40% of insect-related anaphylaxis cases, making them the most common cause in the country.[32] In Brazil, *Polybia paulista* is frequently encountered, and its venom is a well-recognized trigger of anaphylaxis.[58] The second most frequent group linked to Hymenoptera-induced anaphylaxis is *Apidae*.[59] Key species in this group include *Apis mellifera* (honeybees) and *Bombus* species (bumblebees). Allergy to bee venom is common among people with repeated exposure, such as beekeepers, their families, and children.[60] In South Africa, 99% of fatal insect venom reactions are caused by local honeybee species *Apis mellifera capensis* and *Apis mellifera scutellata*.[61] Bumblebees are generally not aggressive, and stings are uncommon in the general population; however, the widespread use of bumblebees for agricultural pollination has increased the number of venom allergies among workers, including cases of anaphylaxis.[55] The formicidae family (ants) can also cause systemic allergic reactions. Notable examples include *Solenopsis invicta* (the imported fire ant) and *Myrmecia pilosula* (the jack jumper ant). *Solenopsis invicta* is now found worldwide and is the most common cause of insect allergies in the southern US.[62] In Australia, *Myrmecia pilosula* is the main cause of severe allergic reactions, with an allergy prevalence of about 3% in certain local communities.[63] There have also been reports of anaphylaxis caused by hematophagous insects. In these cases, salivary proteins are thought to act as allergens, with horse flies and kissing bugs being the most frequently reported sources. Anaphylaxis has also been documented following bites from mosquitoes, tsetse flies, and louse flies.[55] Apart from stings and bites, indoor insect allergens-such as cockroach exposure-have been linked to asthma, and contact allergies caused by caterpillars have also been reported.[64,65] With the recent global rise in interest in eating insects, there is potential for an increase in food allergies caused by edible insects. Insect-related anaphylaxis remains an important public health issue worldwide, with new risks emerging from environmental shifts, workplace exposure, and changing dietary habits.

Others and unknown (idiopathic)

Even with thorough investigations, a significant number of anaphylaxis cases have no clear trigger. Idiopathic anaphylaxis makes up about 6.5-35% of cases, with rates differing across studies.[1] When evaluating patients with repeated episodes of idiopathic anaphylaxis, mastocytosis should be considered as a possible underlying factor. Individuals with systemic mastocytosis are at higher risk of severe anaphylactic reactions, which may appear idiopathic if the mast cell disorder has not been diagnosed.

This underdiagnosis often results from delays in seeking medical attention. Alpha-gal syndrome is a distinct form of delayed food allergy caused by IgE antibodies directed against galactose-α-1,3-galactose (alpha-gal), a carbohydrate present in mammalian meat.

TABLE 5. Classification of Hymenoptera of Clinical Importance for Allergy.

Order	Family	Subfamily	Scientific name	Common name
Hymenoptera	*Apidae*		*Apis melifera*	Honey bee
			Apis dorsata	Giant honey bee
			Bombus spp.	Bumble bee
			Megabombus spp.	
			Pyrobombus spp.	
			Halictus spp.	
			Dialictus spp.	
	Vespidae	*Vespinae*	*Vespula vulgaris*	Yellowjacket Common wasps
			Vespula pensylvanica	Western yellowjacket
			Vespa crabro	European hornet
			Vespa velutina	Asian hornet
			Vespa affinis	Lesser banded hornet
			Vespa orientalis	Oriental hornet
			Dolichovespula arenaria	Yellow hornet
			Dolichovespula maculata	White-faced hornet
		Polistinae	*Polistes* spp.	Paper wasp
			Poybia paulista	
	Formicidae	*Myrmicinae*	*Solenopsis invicta*	Fire ant Imported fire ant
			Solenopsis richteria	Black fire ant
			Pogonomyrmex spp.	Harvester ant
		Myrmiciinae	*Myrmecia* spp.	Jack jumper ant
		Ponerinae	*Pachycondyla* spp.	Samsum ant Chinese needle ant
		Rhytidoponera	*Rhytidoponera metallica*	Green-head ant

Unlike typical food allergies that trigger reactions within minutes, alpha-gal syndrome leads to delayed anaphylaxis that occurs 2-6 hours after eating mammalian meat.[66] This syndrome is mainly linked to tick bites, since tick saliva contains alpha-gal. Repeated exposure to ticks can cause sensitization and the later development of an allergy to mammalian meat.[67] Cases of alpha-gal syndrome have been reported in the US, Europe, Australia, and Japan, and it has become a recognized cause of anaphylaxis in these regions.[68]

INITIAL MANAGEMENT

Severity assessment

Anaphylaxis is a medical emergency requiring prompt recognition and treatment. The first-line therapy for anaphylaxis is the intramuscular administration of adrenaline (epinephrine)[1], regardless of whether the onset occurs in hospital settings or in the community, such as restaurants or schools. Early management is critical, because it significantly affects patient outcomes. Current international guidelines classify anaphylactic reactions into three to five grades, with specific criteria defined for each organ system.[1,69] The Japanese Anaphylaxis Guidelines 2022 use a three-level severity system (Table 6)[70,71], categorizing reactions as mild, moderate, or severe. Adrenaline should be given as soon as anaphylaxis is diagnosed, regardless of its severity; the classification system is mainly intended to guide clinicians in deciding the appropriate level of monitoring and any additional supportive measures needed. Physicians must remain alert, as some patients may still need adrenaline even if they do not fully meet the formal diagnostic criteria for anaphylaxis.

Emergency treatment

Adrenaline should be given without delay to all patients showing respiratory and/or cardiovascular symptoms during an anaphylactic reaction. For example, early administration is appropriate for patients with a history of anaphylaxis who develop severe abdominal symptoms soon after consuming a known allergen.

TABLE 6. Grading of Food-Induced Anaphylaxis According to Clinical Symptom Severity.

Grade	1 (mild)	2 (moderate)	3 (severe)
Skin	Localized urticaria, exanthema, wheal, pruritus	Generalized urticaria, exanthema, wheal, pruritus	-
	Swollen eyelid or lip	Swollen face	-
Gastrointestinal tract	Pruritus of the throat or oral cavity	Throat pain	-
	Mild abdominal pain	Moderate abdominal pain	Cramps
	Nausea, emesis, diarrhea	Recurrent emesis, diarrhea	Continuous emesis, loss of bowel control
Respiratory tract	Intermittent cough, nasal congestion, sneezing, rhinorrhea	Repetitive cough	Persistent cough, hoarseness, "barking" cough
	-	Chest tightness, wheezing detectable via auscultation	Audible wheezing, dyspnea, cyanosis, saturation < 92%, swallowing or speaking difficulties, throat tightness, respiratory arrest
Cardiovascular	-	Pale face, mild hypotension, tachycardia (increase of > 15 beats/min)	Hypotension, dysrhythmia, severe bradycardia, cardiac arrest
Neurological	Change in activity level, tiredness	Light-headedness, feeling of "pending doom," somnolence, headache	Confusion, loss of consciousness, incontinence

The severity score is based on the organ system that is most affected by the symptoms. Hypotension was defined as systolic blood pressure < 70 mmHg for children aged 1 month to 1 year, < 70 + (2 × age) mmHg for children aged 1-10 years, and < 90 mmHg for children aged 11 years to adulthood. Mild hypotension was defined as systolic blood pressure < 80 mmHg for children aged 1 month to 1 year, < 80 + (2 × age) mmHg for children aged 1-10 years, and < 100 mmHg for children aged 11 years to adulthood. Wheezing detected by stethoscopic auscultation was defined as mild wheezing. Audible wheezing was defined as wheezing detected without stethoscopy. The severity score was defined according to Japanese anaphylaxis guidelines.
Min, minutes.

Likewise, prompt use of adrenaline is advised for individuals with asthma, especially those who need ongoing asthma treatment.

In general, the same guidelines for giving adrenaline apply to both healthcare professionals and caregivers. Caregivers who may struggle to accurately assess early signs of severity should be encouraged to administer adrenaline without waiting for reaction to progress to more severe symptoms, since delays in using epinephrine have been linked to fatal outcomes. Despite its importance, adrenaline use remains insufficient.[72] Many patients and caregivers still fail to use adrenaline even after experiencing life-threatening anaphylactic reactions.

The intramuscular route is preferred in all circumstances because it allows for rapid absorption, reaches peak plasma levels in about 10 minutes (min), and has a safer, longer-lasting effect than intravenous administration. The recommended injection site is the anterolateral thigh, which avoids major nerves and arteries. Intramuscular adrenaline (at a 1:1,000 concentration, equal to 1 mg/mL) should be given at a dose of 0.01 mg/kg in children, with a maximum single dose of 0.3-0.5 mg.[1] Doses may be repeated every 5-15 min if symptoms do not respond.[1] Intramuscular administration is generally safe and well-tolerated. In contrast, intravenous adrenaline is usually reserved for intensive care or emergency department use, where continuous cardiac monitoring and experienced medical oversight are available, as this route carries higher risks of arrhythmias and hypertension compared to intramuscular injection. Most international guidelines, including those from the WAO, continue to recommend intramuscular adrenaline as the first-line treatment, reserving intravenous use for severe cases that do not respond or when immediate vascular access is already in place. Although adrenaline is the mainstay of anaphylaxis management, other supportive measures are also vital for the best outcomes. Fluid replacement is especially important in patients with cardiovascular involvement. Rapid intravenous infusion of crystalloids should be started without delay.

Corticosteroids may help reduce the risk of biphasic reactions, although supporting evidence is still limited. Intravenous methylprednisolone or hydrocortisone are commonly given for this purpose. Antihistamines are used as additional therapy but should never replace adrenaline as the first-line treatment. H1 antihistamines can help relieve urticaria and itching, while H2 antihistamines may offer extra benefit for gastrointestinal and cardiovascular symptoms.

Other supportive measures include administering high-flow oxygen and using bronchodilators for patients with bronchospasm. All patients should be placed in a supine position with their legs elevated unless breathing difficulties require them to sit upright.

Some patients may not respond well to standard doses of adrenaline. Beta-blockers are the most common reason of adrenaline resistance,

as they block beta-adrenergic receptors. In these cases, glucagon should be considered because it works independently of these receptors. ACE inhibitors, angiotensin receptor blockers, tricyclic antidepressants, preexisting cardiovascular disease, and older age can also decrease responsiveness to adrenaline.

Management approaches for adrenaline resistance include administering repeated doses of adrenaline, providing aggressive fluid resuscitation, and giving glucagon to patients taking beta-blockers. For cases that do not respond to initial measures, early consultation with intensive care specialists is advised.

LONG-TERM MANAGEMENT

Patients who have had an anaphylactic episode need tailored long-term care. Before being discharged from medical care, they should be given a written anaphylaxis emergency action plan that clearly explains how to use an adrenaline (epinephrine) autoinjector.

Adrenaline autoinjectors

All patients who have experienced food-induced anaphylaxis should either be provided with an adrenaline autoinjector (AAI) or given a prescription for one, along with instructions to obtain it immediately upon discharge. Accidental exposure to the allergenic food is common, so patients must always have immediate access to medication like an AAI to allow prompt self-treatment if needed. However, availability of AAIs remains limited in many countries.[73] There are also concerns about the risk of intraosseous injection when using 0.3 mg AAIs in children weighing under 15 kg. In some areas, 0.1 mg AAIs are offered; where these are not available or not suitable, other options like prefilled adrenaline syringes should be considered.[1]

Alternative devices for self-administering adrenaline

Although AAIs are the standard of care and are endorsed by major international guidelines[1,69], their availability and actual use vary widely across countries.[71] Even when prescribed, the rates of AAI use remain low, ranging from 16% to 32%.[75] Common barriers to AAI use include patient reluctance due to the device's design, fear of needles, pain at the injection site, worry about social embarrassment, and concerns about accidental needle injuries.[75,76]

To address these challenges, alternative methods for administering adrenaline are being developed.[77] Various intranasal and sublingual delivery systems have been investigated to enhance patient compliance and improve outcomes. Among intranasal options, "Neffy," developed by ARS Pharmaceuticals, has shown pharmacokinetic and pharmacodynamic profiles equal to or better than approved injectable forms.[78] Neffy has also demonstrated comparable pharmacokinetics, pharmacodynamics, and safety in children and adults[79], with Phase III trials confirming its effectiveness for treating pediatric anaphylaxis.[80] Notably, its nasal absorption is not affected by simultaneous upper respiratory infections, which supports its practical use.[81] Neffy has been approved by both the European Medicines Agency and the United States Food and Drug Administration for adults and children weighing 30 kg or more.

In addition to Neffy, other intranasal products in development include NDS1c (Bryn Pharma) and FMXIN002 (Nasus Pharma), with clinical studies ongoing.[77]

Therefore, sublingual delivery is an encouraging alternative. "Anaphylm," developed by Aquestive Therapeutics Inc., is the first sublingual film that uses a novel adrenaline prodrug. Compared to intramuscular adrenaline, Anaphylm reaches similar plasma epinephrine levels and has a comparable side effect profile, while achieving peak plasma concentration significantly faster.[82] Its absorption and effectiveness are not notably reduced when taken immediately after eating, which supports its practical use for managing food-related anaphylaxis.[83]

Furthermore, Zeneo® (Crossject, France) is an innovative, prefilled, single-use, needle-free autoinjector that can deliver fixed doses intradermally, subcutaneously, or intramuscularly.[84] Devices like Zeneo® expand options for administering adrenaline and could serve as valuable tools in anaphylaxis management.

Since adrenaline remains the first-line treatment for anaphylaxis and must be given quickly, developing and expanding the use of new delivery methods is essential to ensure timely and effective administration, especially for individuals who are reluctant to use conventional AAIs.

Despite progress in diagnosing and managing anaphylaxis, several challenges persist. Raising awareness and providing education for patients, caregivers, and healthcare professionals are vital to support early recognition and correct use of adrenaline. Improving global access to AAIs and alternative delivery systems is also necessary to address barriers to treatment. Additional research is needed to clarify the mechanisms behind anaphylaxis, especially in adult-onset cases and those with unusual features. Work on predictive biomarkers and preventive measures, including immunomodulatory therapies, offers a promising path forward for improving anaphylaxis care.

Immunomodulation

Allergen immunotherapy has a proven role in preventing anaphylactic reactions to certain allergens, such as insect venom and specific medications, and new evidence suggests it may also help prevent food-induced anaphylaxis.[45,85-87]

Venom immunotherapy

Venom immunotherapy (VIT) is an established treatment for individuals with Hymenoptera venom allergies who are at risk of severe systemic reactions. VIT works by administering gradually increasing doses of venom extract subcutaneously to build immune tolerance. Multiple studies have demonstrated that VIT provides long-lasting protection, with success rates > 90% in preventing systemic reactions from future stings.[88,89] Consequently, VIT is regarded as the standard treatment for patients with venom-induced anaphylaxis.[66] European Academy of Allergy and Clinical Immunology (EAACI) for insect venom allergy and to assess the effectiveness, cost-effectiveness, and safety of VIT.[90] Although the evidence base was limited in size and quality, a meta-analysis found that VIT greatly lowered the risk of future severe systemic reactions [odds ratio, 0.08;

95% confidence interval (CI), 0.03-0.26] and significantly improved disease-specific quality of life (risk difference, 1.41; 95% CI, 1.04-1.79).[90] Mild side effects occurred during both the build-up and maintenance phases, but no deaths were reported in the studies reviewed. Early evidence also indicates that VIT is probably cost-effective for individuals at high risk of repeated systemic reactions or those with reduced quality of life, although additional health economic analyses are needed.

The EAACI guidelines offer practical recommendations for administering VIT to both adults and children.[85] VIT is advised for patients who experience systemic sting reactions beyond widespread skin symptoms and for adults with generalized skin symptoms alone when these significantly affect quality of life. In contrast, VIT is not recommended for individuals who have only large local reactions or for those with sensitization discovered incidentally but without systemic symptoms. Taking H1 antihistamines beforehand is recommended to help minimize local and systemic side effects. A minimum treatment period of 3 years is advised, with extension to ≥ 5 years for patients who had severe initial reactions. Lifelong VIT may be appropriate for people with high exposure risk, those with severe initial reactions, or individuals who develop systemic side effects during therapy.

Although the supporting evidence for VIT is stronger in adults, pediatric age should not be viewed as a barrier. Contrary to common misconceptions, many children do not naturally outgrow venom allergies, and VIT has been shown to enhance safety and quality of life in this group. However, key knowledge gaps remain, including the need for more research involving children, older adults, and people with cardiovascular conditions, along with studies on predictive biomarkers, cost-effectiveness, and reasons for treatment failure. To aid its wider use, the EAACI guidelines highlight the importance of identifying suitable patients in primary care and raising awareness among healthcare professionals, funding bodies, and patient organizations. VIT continues to be one of the most effective disease-modifying options for anaphylaxis and should be used whenever appropriate.

Drug desensitization

Drug desensitization protocols are used for patients who have immediate HSRs to critical medications such as antibiotics, chemotherapy drugs, or biologic agents.[91] This process involves administering the culprit drug in gradually increasing doses under close medical supervision to induce temporary immune tolerance. Although this does not produce permanent immune changes, it makes it possible for patients with drug-induced anaphylaxis to safely receive first-line treatments. This method is commonly used in clinical practice, especially for β-lactam antibiotics and chemotherapy drugs.[92]

Any drug can potentially cause HSRs. Once an allergological assessment confirms drug hypersensitivity, simply avoiding the drug and replacing it with an unrelated alternative is often enough. However, when stopping the culprit drug would adversely affect survival, treatment effectiveness, or quality of life, desensitization should be viewed as a standard treatment option rather than an exception. Importantly, pediatric age should not be seen as a barrier. Drug desensitization can be performed safely and effectively in children, improving survival and clinical results.[87] While the general principles for desensitization are similar for all age groups, pediatric cases require additional attention to age-specific protocols, physiological factors, and technical details.

The WAO Committee Statement highlighted the critical role of rapid drug desensitization (RDD) as a life-saving measure, especially for intravenous medications like antibiotics, chemotherapy drugs, and biologics.[91] RDD allows patients to keep receiving first-choice treatments and reduces the need for alternatives that may be less effective or have greater toxicity. For example, at Ramon y Cajal University Hospital in Spain, the number of RDD procedures rose by about 30% over 10 years, with an 85% increase in intravenous drug provocation tests during the same timeframe.[93] Furthermore, survival rates for patients undergoing RDD were similar to those of patients without allergies receiving standard chemotherapy, indicating that RDD does not diminish cancer treatment efficacy.

Food-induced anaphylaxis

Allergen immunotherapy can help prevent food-induced anaphylaxis by raising the threshold for clinical reactions and encouraging immune tolerance. Similar to how VIT is used for insect sting anaphylaxis, controlled exposure to allergens has been studied as a way to lower the risk of severe reactions in people with food allergies.[94] The goal is to increase the amount of allergen that can be consumed without causing serious symptoms, thus decreasing the chance of anaphylaxis due to accidental ingestion.[95] Although oral immunotherapy (OIT) is not yet advised for routine practice because of concerns about its safety and standardization,[96,97] clinical data support its effectiveness for certain patients with food-induced anaphylaxis. For instance, in cow's milk allergy, low-dose OIT led to about one-third of patients achieving short-term sustained unresponsiveness after 12 months of treatment[98], with further improvement seen over a 3-year follow-up.[99] Comparable positive outcomes have been found for hen's egg, wheat, and peanut allergies.[100-105] Beyond showing clinical benefit, OIT has been linked to a very low rate of severe adverse reactions that would require adrenaline use during home treatment (0.0-0.04%). Successfully completed OIT may lower the risk of anaphylaxis from accidental allergen exposure.[86]

Biologics

Biologic treatments have emerged as promising new approaches to boost allergen tolerance and lower the risk of severe reactions.[106,107] Among these, omalizumab-a monoclonal antibody that targets IgE-has been widely studied both as a standalone treatment and as an add-on therapy for people with food allergies.[108] This advancement could broaden future options for long-term anaphylaxis management.

Omalizumab, an anti-IgE monoclonal antibody, has shown to be effective and safe when used alone in individuals with multiple food allergies. In a recent randomized controlled trial, participants aged 1-55 years with peanut allergies and at least two other food

allergies (e.g., cashew, milk, egg, walnut, wheat, or hazelnut) were enrolled.[108] Individuals who reacted to ≤ 100 mg of peanut protein and ≤ 300 mg of two other foods during screening were randomized in a 2:1 ratio to receive subcutaneous omalizumab or placebo for 16-20 weeks. Of the 177 children and adolescents analyzed, 67% of those treated with omalizumab could tolerate at least 600 mg of peanut protein without severe symptoms, compared with just 7% in the placebo group ($p < 0.001$). Omalizumab also significantly increased tolerance to cashew (41% vs. 3%), milk (66% vs. 10%), and eggs (67% vs. 0%). Safety outcomes were similar overall, except for more injection site reactions in the omalizumab group. These results indicate that omalizumab monotherapy can effectively raise reaction thresholds for various food allergens and may offer a valuable treatment choice for patients with multiple food-induced anaphylaxis, improving quality of life and reducing the risk of severe reactions.

Beyond food allergies, the possible use of omalizumab in treating drug-induced anaphylaxis has also been explored. HSRs to chemotherapy drugs can prevent patients from receiving optimal first-line treatments and can negatively impact oncological outcomes. Although RDD is often used in these situations, breakthrough reactions may still occur. Omalizumab is not yet approved for use during chemotherapy desensitization, but small studies have indicated that administering omalizumab beforehand could improve the safety and effectiveness of desensitization protocols.[109] Suggested approaches include giving omalizumab before the first desensitization procedure and ahead of each chemotherapy cycle. More research is needed to develop standardized protocols, but omalizumab could provide a valuable additional option for patients at high-risk of drug-induced anaphylaxis who have few other choices. Therefore, omalizumab represents an important potential advance in the long-term management of anaphylaxis, with possible applications that reach beyond food allergies to include drug-related reactions.

Recent findings indicate that dupilumab, a monoclonal antibody that blocks the IL-4 receptor α subunit, may affect food-induced anaphylaxis through its immunomodulatory actions. In a Phase II trial, dupilumab lowered both total and peanut-specific IgE levels by around 50%, but only 8.3% of participants were able to tolerate peanut in an oral food challenge after 24 weeks.[110] When used together with peanut OIT, dupilumab resulted in a 20.2% increase in the proportion of children able to tolerate a higher amount of peanut protein compared to OIT alone. However, it did not decrease the incidence of anaphylaxis related to OIT.[111] Although dupilumab shows encouraging immunomodulatory effects in individuals with food allergies, as shown by consistent reductions in allergen-specific IgE levels, its ability to achieve clinical tolerance or reduce allergic reactions is still limited and warrants further study in larger trials.

CONCLUSION

Anaphylaxis is a severe, potentially life-threatening HSR whose global incidence is rising. Common triggers differ by age and region, with food, medications, and insect venom being the main causes. In several countries, drug-induced anaphylaxis accounts for the highest number of fatal cases. Rapid intramuscular injection of adrenaline is vital, yet its use remains insufficient in both medical and community settings. Long-term strategies include allergen immunotherapy for venom and drug triggers, OIT for selected food allergies, and emerging biologics like omalizumab. These interventions can increase tolerance and lower the risk of severe reactions but face barriers related to cost, availability, and clinician experience. Enhancing patient education, expanding access to AAIs, and developing easier-to-use delivery systems are necessary to improve management. Future priorities should include addressing knowledge gaps and applying personalized multidisciplinary care, especially for high-risk groups such as children and older adults.

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