

Anaphylaxis

Definition, Epidemiology, Diagnostic Challenges, Grading System



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KEYWORDS

• Anaphylaxis • Epinephrine • Allergic reactions • Systemic reactions

KEY POINTS

- Anaphylaxis is a syndrome without a universally accepted definition.
- A more sensitive definition of anaphylaxis is offered to promote the early administration of epinephrine.
- The incidence and prevalence of anaphylaxis have increased in the last 2 decades.
- IM epinephrine is the only effective therapy for anaphylaxis and is more effective with use at the earliest point in the development of anaphylaxis.
- Most anaphylaxis events resolve spontaneously but progression to a serious reaction is not consistently predictable supporting the use of IM epinephrine before the development of life-threatening signs.

INTRODUCTION

Medical definitions serve 2 purposes: to improve communication and facilitate clinical decision making. Anaphylaxis is a syndrome lacking a universally accepted definition. Most anaphylaxis definitions focus on specificity, to avoid mislabeling nonlife threatening, systemic reactions as anaphylaxis. For real-time, clinical decision making, the authors of this article prefer a more sensitive definition to encourage early treatment and monitoring of reactions that *may* become life-threatening. This approach uses the World Allergy Organization Grading Criteria for Systemic Allergic Reactions, shown in **Table 1**, to identify manifestations that may progress to more serious reactions.¹ The acute allergic reaction grading system proposed by Dribin and colleagues also uses a similar scoring system and provides caveats that the grade may change rapidly and the grading system does not dictate or direct management decisions.²

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Table 1
Modified WAO grading for systemic allergic reactions

Grades				
Confirmed Anaphylaxis				
Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Symptom(s)/sign(s) from one organ system Cutaneous • Urticaria and/or erythema-warmth and/or pruritus other than localized at the injection site And/or • Lip tingling or itching or • Angioedema (not laryngeal) Or Upper respiratory • Nasal Symptoms: sneezing, rhinorrhea, pruritus, and/or nasal congestion And/or • Throat clearing (itchy throat) And/or • Cough not related to bronchospasm Or Conjunctival • Erythema, pruritus, tearing Or Other • Nausea • Metallic taste	Symptom(s)/sign(s) From ≥ 2 organ symptoms listed in grade 1	Lower airway • Mild bronchospasm (cough, wheezing, shortness of breath) which responds to treatment And/or Gastrointestinal • Abdominal cramps and/or vomiting/diarrhea Other • Uterine cramps • Any symptom(s)/sign(s) from grade 1 would be included	Lower airway • Severe bronchospasm not responding or worsening in spite of treatment And/or Upper airway • Laryngeal edema with stridor • Any symptom(s)/sign(s) from grades 1 or 3 would be included	Lower or upper airway • Respiratory failure And/or Cardiovascular • Collapse/hypotension And/or • Loss of consciousness (vasovagal excluded) • Any symptom(s)/sign(s) from grades 1, 3, or 4 would be included

The final grade of the reaction is not determined until the event is over, regardless of the medication administered to treat the reaction. The final report should include the first symptom(s)/sign(s) and the time of onset after the causative agent exposure and a suffix reflecting if and when epinephrine was or was not administered: a, ≤ 5 min; b, greater than 5 min to ≤ 10 min; c, greater than 10 to ≤ 20 min; d, greater than 20 min; z, epinephrine not administered. Final report: Grade 1 to 5; a-d, or z; First symptom(s)/sign(s); Time of onset of first symptom(s)/signs(s).

Modified from Cox LS, Sanchez-Borges M, Lockey RF. World Allergy Organization Systemic Allergic Reaction Grading System: Is a Modification Needed? J Allergy Clin Immunol Pract. 2017 Jan-Feb;5(1):58-62.e5.

Our intent is to inform health care management decisions and to advocate for the utilization of intramuscular (IM) epinephrine, a therapy with very little risk, before serious physiologic dysfunction; dysfunction that fulfills criteria for most definitions of anaphylaxis. There are limited data to prove epinephrine treatment before serious manifestations are always beneficial, and all clinicians do not agree that systemic hypersensitivity reactions progress to anaphylaxis with sufficient frequency to justify the anticipatory use of epinephrine. Early epinephrine administration does not imply treatment before symptoms or signs but rather with manifestation onset, in the anticipation of potential progression. Concerns about early or premature epinephrine use in an unsupervised setting do not necessarily apply to treatment in a health care environment.³ Epinephrine is the most effective treatment of anaphylaxis; however, it is underutilized.⁴ Delayed epinephrine administration is cited as a contributor to anaphylaxis fatality.⁵ Therefore, the authors of this article prefer to encourage epinephrine use before severe respiratory or cardiovascular dysfunction. Whether milder reactions are labeled as “mild anaphylaxis” or lower grades of systemic hypersensitivity or allergic reactions is only of semantic concern if epinephrine is used before life-threatening signs.

DEFINITION

Anaphylaxis is a syndrome with potentially multiple features. Validating specific findings, severity, or system involvement required for the diagnosis is problematic, as double-blind studies without epinephrine therapy are not ethical and there is overlap between systemic hypersensitivity reactions and anaphylaxis.² Thus, most definitions are evaluated in retrospective cohorts or registries and not prospectively.¹ The absence of prospective data adds to the controversy concerning the optimal definition.

The editors of this book prefer an inclusive anaphylaxis definition and an expansion of the grading system for systemic allergic reactions developed by the World Allergy Organization.¹ A broader, clinical anaphylaxis definition for clinical decision making encourages epinephrine for all grades of systemic reactions. Grade 5 is life-threatening and would be accepted as anaphylaxis by all definitions. Anaphylaxis is a potentially life-threatening syndrome; however, life-threatening manifestations are *not necessary* to justify IM epinephrine.^{3,6} The treatment of choice for lower grades of systemic hypersensitivity reactions is IM epinephrine, before life-threatening features, unless the clinical situation clearly provides reassurance that progression is extremely unlikely. Features that predict more severe systemic reactions help in the assessment as to the need for epinephrine during milder signs and symptoms.⁶ Factors that predict more severe anaphylaxis include onset in close proximity to the time of allergen exposure, injected culprit antigen (eg, medications, insect allergens) as opposed to ingested, a history of mast cell disorders, advanced age, beta-blockers, and angiotensin pathway inhibitor therapy, and asthma.⁶ The authors indicate that IM epinephrine 0.01 mg/kg is sufficiently safe to administer in almost all systemic hypersensitivity reactions, whether milder manifestations are defined as mild anaphylaxis or systemic reactions.

Variability in Current Definitions

Definitions of anaphylaxis currently in the medical literature are listed in [Table 2](#).⁷ The words serious or severe, life-threatening, rapid, and systemic are common terms to all definitions. Hypersensitivity is preferred to allergy in 5 of the 6, most likely because anaphylaxis is not dependent on a specific immune response. The National Institute

Table 2
Definitions of anaphylaxis currently in the medical literature

WAO 2011	EAACI 2013	AAAAI/ACAAI 2010	ASCIA 2016	NIAID 2006	WHO ICD-11 2019
A serious life-threatening generalized or systemic hypersensitivity reaction.	A severe life-threatening generalized or systemic hypersensitivity reaction.	An acute life-threatening systemic reaction with varied mechanisms, clinical presentations, and severity that results from the sudden release of mediators from mast cells and basophils	Any acute onset illness with typical skin features (urticarial rash or erythema/flushing, and/or angioedema), PLUS involvement of respiratory and/or cardiovascular and/or persistent severe gastrointestinal symptoms; or Any acute onset of hypotension or bronchospasm or upper airway obstruction whereby anaphylaxis is considered possible, even if typical skin features are not present.	Anaphylaxis is a serious allergic reaction that involves more than one organ system (for example skin, respiratory tract, and/or gastrointestinal tract). It can begin very rapidly, and symptoms may be severe or life-threatening	Anaphylaxis is a severe, life-threatening systemic hypersensitivity reaction characterized by being rapid in onset with potentially life-threatening airway, breathing, or circulatory problems and is usually, although not always associated with skin and mucosal changes.
A serious allergic reaction that is, rapid in onset and might cause death	An acute, potentially fatal, multi-organ system, allergic reaction				

Abbreviations: AAAAI/ACAAI, American Academy of Allergy; Asthma and Immunology/American College of Allergy, Asthma; and immunology; ASCIA, Australasian Society of Clinical Immunology and Allergy; EAACI, European Academy of Allergy and Clinical Immunology; NIAID, National Institute Of Health And Infectious Diseases; WAO, World Allergy Organization; WHO ICD-11, World Health Organization International Classification of Diseases 11th edition.

From Cardona V, Ansotegui IJ, Ebisawa M, El-Gamal Y, Fernandez Rivas M, Fineman S, Geller M, Gonzalez-Estrada A, Greenberger PA, Sanchez Borges M, Senna G, Sheikh A, Tanno LK, Thong BY, Turner PJ, Worm M. World allergy organization anaphylaxis guidance 2020. *World Allergy Organ J.* 2020 Oct 30;13(10):100472.

of Allergy and Infectious Disease (NIAID) definition does specify allergy. Skin manifestations are mentioned in 3 of the 6, and the other 3 state that multiple systems are involved. Five of the 6 state that anaphylaxis is life-threatening although the World Health Organization definition, 1 of the 5, subsequently states it is “potentially life-threatening.” Two of the 6 state that mediators of basophils and mast cells are involved, and the NIAID definition implies this as allergic or immunologic anaphylaxis depends on mast cells and/or basophils. A definition that classifies anaphylaxis as presenting in more than one system would not include cases of severe anaphylaxis that present with the involvement of only 1 system, for example, cardiovascular collapse in perianesthetic anaphylaxis without evident cutaneous, respiratory, or gastrointestinal manifestations.⁸ To define anaphylaxis as a serious life-threatening event is too limited. Fatal and near-fatal anaphylaxis events are extremely rare.^{7,9} More than 90% to 99% of anaphylactic reactions or suspected reactions resolve without treatment.¹⁰ However, it is nearly impossible to accurately predict the likelihood of the clinical progression of hypersensitivity reactions or mild anaphylaxis.

The World Allergy Organization (WAO) classifies anaphylaxis as a serious life-threatening generalized or systemic hypersensitivity reaction. WAO grades systemic hypersensitivity reactions on a scale of 1 to 5, whereby 4/5 on the scale is classified as anaphylaxis (see [Table 1](#)). A Delphi process has been used for acute allergic reactions across a spectrum between mild and life-threatening allergic reactions that can be anaphylactic or nonanaphylactic.^{11,12} Thus, anaphylaxis is either a continuum, with milder forms, or is the end result of a systemic hypersensitivity reaction. Both approaches are acceptable if epinephrine is used as the preferred therapy in all but the very mildest systemic hypersensitivity reactions.

Proposed Definition

The anaphylaxis definition the editors propose for this book is the following:

Anaphylaxis is a potentially serious, systemic reaction, either immunologic or non-immunologic, that is usually rapid in onset, is of variable severity, is responsive to the timely administration of epinephrine, and rarely causes death. Severe anaphylaxis is characterized by the compromise of breathing and/or circulation and most often, but not always, progresses from and is preceded by milder signs/symptoms. Cutaneous manifestations, including generalized pruritus, flushing, and urticaria, are the most common initial features of anaphylaxis

The authors support epinephrine 0.01 mg/kg IM as the primary treatment of systemic hypersensitivity reactions Grades 1 to 3, alternatively termed mild anaphylaxis, before the development of life-threatening manifestations of Grade 4/5. Antihistamine therapy or observation may be considered for Grade 1 or 2 hypersensitivity reactions, although grades can change rapidly, and antihistamine therapy is of little or no use other than to eventually eliminate the symptoms of itching. An antihistamine is not a substitute for epinephrine. Epinephrine should be administered when such symptoms and signs appear rapidly following a known allergen injection or if there is any doubt as to the potential risk of the reaction becoming more severe.

ALLERGIC VERSUS NONALLERGIC

The term anaphylaxis was first used in 1902 by Paul Portier and Charles Richet based on the specific, aberrant allergic reaction of dogs to Portuguese man-of-war toxin injections (Portier P, Richet C. *De l'action anaphylactique de certains venins*. *C R Séances Soc Biol* 1902;54:170). Prior investigators in the mid to late nineteenth

century had described similar adverse immune effects in different animals using egg albumin, diphtheria toxin, heterologous animal sera, and eel extracts, but they did not recognize the specific immune characteristics. Observations from these early studies revealed variability in the physiologic presentation, or shock organ, in various animals experiencing anaphylaxis. This historical connection with allergy has resulted in a frequent, erroneous assumption that all anaphylaxis is an allergic event due to specific IgE triggering mast cell or basophil granule mediator release. Retrospective cohorts do show that most of the anaphylaxis in children and adults is allergic.^{13,14}

Nonallergic anaphylaxis is attributed to the degranulation of mast cells or basophils via mechanisms not dependent on a specific immune response. These nonallergic forms of anaphylaxis include idiopathic, exercise-dependent, radiocontrast reactions, and some drug reactions, including most forms of nonsteroidal anti-inflammatory drug (NSAID) anaphylaxis.^{15,16} Because both allergic and nonallergic anaphylaxis are related to mast cell/basophil degranulation, albeit by differing mechanisms, supports the same treatment of both allergic and nonallergic anaphylaxis. The prior term for nonallergic anaphylaxis is *anaphylactoid*; however, as the treatments for the 2 mechanisms are the same, the current preference is to use the term “nonallergic anaphylaxis” rather than “anaphylactoid.”

There is a limited value of pretreatment with antihistamine and/or corticosteroid in reducing the occurrence or severity of anaphylaxis despite the importance of mast cell and basophil mediators, including histamine. The use of ineffective therapy, such as antihistamines, following the onset of anaphylaxis or systemic hypersensitivity reactions, may delay the use of more effective IM epinephrine.⁷ Antihistamine pretreatment is more likely beneficial in nonallergic anaphylaxis.¹⁷ Antihistamines, both H1 and H2, and corticosteroid therapy do not sufficiently block the number of mediators from mast cells/basophils to prevent anaphylaxis in IgE-mediated reactions.

Allergic anaphylaxis is more likely to be life-threatening than nonallergic, but both may cause death and are treated with IM epinephrine.⁸ The major advantage in a thorough assessment of prior anaphylaxis by an allergist/immunologist is to identify culprits that may be avoided or to determine if allergen immunotherapy or desensitization could reduce future risk.

BIPHASIC, PERSISTENT, AND REFRACTORY ANAPHYLAXIS

Definitions of anaphylaxis focus on the rapid onset, within minutes and rarely up to hours, after exposure to the culprit allergen or circumstances responsible for anaphylaxis. Biphasic anaphylaxis is defined as a reoccurrence of anaphylaxis signs and symptoms without additional exposure to the provocateur.¹⁸ The time between initial symptom/sign resolution and the reoccurrence of signs/symptoms is variable for biphasic anaphylaxis, but the range of 1 to 48 hours was accepted by Dribin and colleagues.² The variability in biphasic anaphylaxis occurrence, 1% to 19%, probably reflects the lack of consistently applied diagnostic criteria. Accurately predicting biphasic anaphylaxis is not generally possible. However, delay in the first dose of epinephrine shows an odds ratio of 2.29 (confidence interval (CI): 1.09–4.79) in predicting the occurrence of biphasic anaphylaxis.¹⁹

Persistent anaphylaxis is a term used to describe anaphylaxis that persists for more than 4 hours after onset, independent of management of the initial reaction; whereas, refractory anaphylaxis is persistent anaphylaxis despite treatment with IM epinephrine 0.01 mg/kg or a maximum single dose of 0.5 mg.² The number of doses or total dose of epinephrine sufficient to categorize anaphylaxis as persistent again is variable, with a Delphi process concluding that 3 or more “doses” or the use of intravenous (IV)

epinephrine without resolution is sufficient to identify refractory anaphylaxis. Additional medical management, such as inhaled beta-agonists, oxygen, and high volume IV colloid should be used as indicated, in addition to the epinephrine, to qualify as refractory anaphylaxis. In contrast to biphasic anaphylaxis, there is no evidence that the early utilization of epinephrine is beneficial in preventing persistent or refractory anaphylaxis, but common sense would dictate it is likely to be beneficial.

EPIDEMIOLOGY

The incidence and prevalence of anaphylaxis have increased during the past 10 to 20 years. Whether the higher incidences of anaphylaxis are due to an actual increase in anaphylaxis or due to improvement in the identification of the syndrome by clinicians remains debatable.²⁰ The variability in anaphylactic definitions limits consistency among epidemiologic studies. Both under-recognition and over-diagnosis will obfuscate studies of a syndrome without a defining characteristic.⁹ Publications document the latest incidence of anaphylaxis between 50 and 112 episodes per 100,000 persons in 1 year. Prevalence is documented between 0.3% and 5.1%.¹⁰

Childhood Anaphylaxis

Anaphylaxis in childhood is more common in younger children between the ages of 0 and 4 years. Pediatric anaphylaxis more commonly occurs after the ingestion of foods by an allergic individual, with cow's milk, peanut, and hen egg being the most common allergens.¹⁰ Insect allergy follows food allergy as the next common cause in childhood, when the geographic location is taken into account.²¹

Adult Anaphylaxis

Anaphylaxis in adults is most commonly attributed to drug allergy and insect sting allergy. Notably, reactions differ between young adults and older adults.²² Administration of drugs by parenteral routes increases the risk of fatality. Some retrospective studies suggest that idiopathic anaphylaxis is the most common cause of adult cases²³. The recognition of delayed anaphylaxis from the ingestion of alpha-

Annual incidence of fatal anaphylaxis in an unselected population

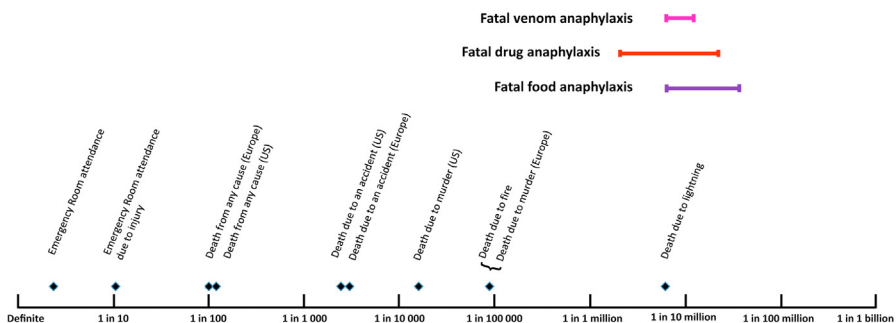


Fig. 1. Estimated rates of fatal drug, food, and venom anaphylaxis compared with other risks for the general population. Reference risks are for the US population unless otherwise stated. Colored bars represent the range of estimates from recent population-based studies of fatal anaphylaxis. (From Turner PJ, Jerschow E, Umasunthar T, Lin R, Campbell DE, Boyle RJ. Fatal Anaphylaxis: Mortality Rate and Risk Factors. *J Allergy Clin Immunol Pract.* 2017 Sep-Oct;5(5):1169-1178.)

Annual incidence of fatal anaphylaxis in food or venom allergic individuals

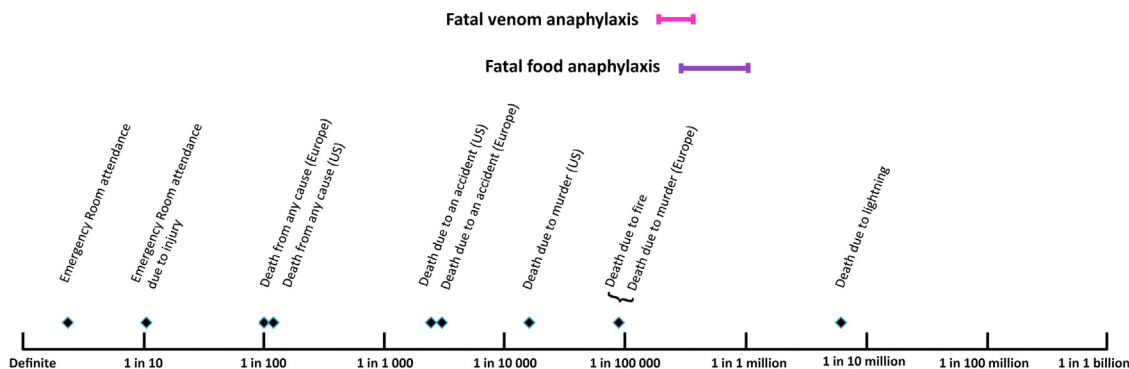


Fig. 2. Estimated rates of fatal food and venom anaphylaxis for people with known food allergy or insect venom allergy. Reference risks are for the US population unless otherwise stated. Data shown for individuals with food allergy are the 95% confidence interval of fatal food anaphylaxis risk, derived from the systematic review of.²⁷ Data shown for individuals with insect venom allergy were calculated using the range of estimates from recent population-based studies of fatal venom anaphylaxis, and an estimated 3% population prevalence of insect venom allergy.²⁶ (From Turner PJ, Jerschow E, Umasunthar T, Lin R, Campbell DE, Boyle RJ. Fatal Anaphylaxis: Mortality Rate and Risk Factors. *J Allergy Clin Immunol Pract.* 2017 Sep-Oct;5(5):1169-1178.)

galactose- α -galactose, a carbohydrate found in most mammalian meat (pork, beef, mutton) but not present in catarrhine mammals (humans and old world primates), fish, or fowl. The anaphylaxis from this carbohydrate occurs 4 to 6 hours after ingestion in allergic subjects and is an IgE-mediated allergic reaction.²⁴ The delay in the anaphylaxis originally limited the recognition of this allergen as a cause. Following the characterization of this syndrome, many of the idiopathic cases in adult anaphylaxis surveys are now attributed to alpha-galactose- α -galactose allergy.¹³ Evidence demonstrates that tick bites in the United States are responsible for the exposure to alpha-galactose- α -galactose resulting in specific IgE responsible for the allergic reaction to red meat.²⁵ The rationale for the delay in symptoms is not clear.

Fatal Anaphylaxis

The incidence of anaphylaxis death in the general population is rare, and the mortality incidence among subjects with known allergy or prior anaphylaxis is uncommon.⁵ Estimates of mortality from anaphylaxis in the general population approximate the risk of death from lightning strikes, about 1:9,000,000, **Fig. 1**.⁵ Mortality in the population with documented allergy to insect venom or food approximates the death rate from fire or murder in Europe, about 1:500 to 900,000, **Fig. 2**.⁵ Fatal anaphylaxis from insect stings is more common in subjects over 60 years, whereas fatal anaphylaxis from food allergens is more common in the second and third decades of life.²² Older adults with comorbidities, particularly cardiovascular disease, are at increased risk of death in general, particularly to medications and insect stings.⁵ Also, the mortality of anaphylaxis in the perioperative setting is greater than other scenarios, likely due to physiologic dysfunction associated with anesthesia and surgery.⁸ Many, but not all, deaths from anaphylaxis were preceded by nonfatal episodes.¹⁰ The correct diagnosis, counseling of affected subjects, and provision of epinephrine auto-injectors are important to limit fatalities.³

SUMMARY

Definitions of syndromes are problematic as there are no definitive tests or findings to prove or exclude the diagnosis. Anaphylaxis is usually sudden in onset, not expected, and not amenable to blinded, evidentiary human studies. The definition of anaphylaxis should be clinically useful and understandable for all or most stakeholders, including health professionals, the public, and policy makers. Regardless of the strategy to define the condition, the prompt use of safe and effective IM epinephrine is essential. Early recognition of potential anaphylaxis, monitoring of vital signs and symptoms, and prompt use of epinephrine optimize acute outcomes. Identification of the culprit is important to avoid or limit subsequent occurrences of this potentially life-threatening condition.

CLINICS CARE POINTS

- When monitoring patients for manifestations that indicate possible anaphylaxis be vigilant for generalized urticaria, pruritus, nasal congestion and rhinorrhea, nausea, abdominal cramps, chest tightness, throat clearing, and cough. A vague sensation of an impending problem is not unusual at the onset. Children may demonstrate vomiting as a primary manifestation.
- Hypotension without skin symptoms is suggestive of a mast cell disorder predisposing to anaphylaxis.

- Risk factors for a greater likelihood of progression to severe anaphylaxis include allergen exposure by injection, symptom onset in close proximity to causal exposure, preexisting asthma, mast cell disorder, and delay in the administration of IM epinephrine following the onset of symptoms.
- Anaphylaxis mortality is associated with older age, cardiovascular disease, treatment with beta-blockers or angiotensin inhibiting drugs and mast cell disorders.

DISCLOSURE

The authors have nothing to disclose that has a direct financial interest in the subject matter or materials discussed.

REFERENCES

1. Barg W, Medrala W, Wolanczyk-Medrala A. Exercise-induced anaphylaxis: an update on diagnosis and treatment. *Curr Allergy Asthma Rep* 2011;11(1):45–51.
2. Cardona V, Ansotegui IJ, Ebisawa M, et al. World allergy organization anaphylaxis guidance 2020. *World Allergy Organ J* 2020;13(10):100472.
3. Commins SP, James HR, Kelly LA, et al. The relevance of tick bites to the production of IgE antibodies to the mammalian oligosaccharide galactose- α -1,3-galactose. *J Allergy Clin Immunol* 2011;127(5):1286–93.e6.
4. Commins SP, Satinover SM, Hosen J, et al. Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose- α -1,3-galactose. *J Allergy Clin Immunol* 2009;123(2):426–33.
5. Cox LS, Sanchez-Borges M, Lockey RF. World allergy organization systemic allergic reaction grading system: is a modification needed? *J Allergy Clin Immunol Pract* 2017;5(1):58–62.e5.
6. Dribin TE, Schnadower D, Spergel JM, et al. Severity grading system for acute allergic reactions: a multidisciplinary Delphi study. *J Allergy Clin Immunol* 2021;148(1):173–81.
7. Farnam K, Chang C, Teuber S, et al. Nonallergic drug hypersensitivity reactions. *Int Arch Allergy Immunol* 2012;159(4):327–45.
8. Hogan SP. Severity grading system for acute allergic reactions-time for validation and assessment of best practices. *J Allergy Clin Immunol* 2021;148(1):86–8.
9. Mali S. Anaphylaxis during the perioperative period. *Anesth Essays Res* 2012;6(2):124–33.
10. Pattanaik D, Lieberman P, Lieberman J, et al. The changing face of anaphylaxis in adults and adolescents. *Ann Allergy Asthma Immunol* 2018;121(5):594–7.
11. Prince BT, Mikhail I, Stukus DR. Underuse of epinephrine for the treatment of anaphylaxis: missed opportunities. *J Asthma Allergy* 2018;11:143–51.
12. Tanno LK, Bierrenbach AL, Simons FER, et al. Critical view of anaphylaxis epidemiology: open questions and new perspectives. *Allergy Asthma Clin Immunol* 2018;14:12.
13. Tejedor Alonso MA, Moro Moro M, Múgica García MV. Epidemiology of anaphylaxis. *Clin Exp Allergy* 2015a;45(6):1027–39.
14. Tejedor-Alonso MA, Moro-Moro M, Múgica-García MV. Epidemiology of anaphylaxis: contributions from the last 10 years. *J Investig Allergol Clin Immunol* 2015b;25(3):163–75 [quiz follow 174–165].
15. Trcka J, Schmidt C, Seitz CS, et al. Anaphylaxis to iodinated contrast material: nonallergic hypersensitivity or IgE-mediated allergy? *AJR Am J Roentgenol* 2008;190(3):666–70.

16. Turner PJ, Baumert JL, Beyer K, et al. Can we identify patients at risk of life-threatening allergic reactions to food? *Allergy* 2016;71(9):1241–55.
17. Turner PJ, DunnGalvin A, Hourihane JO. The emperor has no symptoms: the risks of a blanket approach to using epinephrine autoinjectors for all allergic reactions. *J Allergy Clin Immunol Pract* 2016;4(6):1143–6.
18. Turner PJ, Gowland MH, Sharma V, et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992–2012. *J Allergy Clin Immunol* 2015;135(4):956–63.e1.
19. Turner PJ, Jerschow E, Umasunthar T, et al. Fatal anaphylaxis: mortality rate and risk factors. *J Allergy Clin Immunol* 2017;5(5):1169–78.
20. Webb LM, Lieberman P. Anaphylaxis: a review of 601 cases. *Ann Allergy Asthma Immunol* 2006;97(1):39–43.
21. Worm M, Moneret-Vautrin A, Scherer K, et al. First European data from the network of severe allergic reactions (NORA). *Allergy* 2014;69(10):1397–404.
22. Wright CD, Longjohn M, Lieberman PL, et al. An analysis of anaphylaxis cases at a single pediatric emergency department during a 1-year period. *Ann Allergy Asthma Immunol* 2017;118(4):461–4.
23. Alqurashi W, Stiell I, Chan K, et al. Epidemiology and clinical predictors of biphasic reactions in children with anaphylaxis. *Ann Allergy Asthma Immunol* 2015;115(3):217–23.e2.
24. Dribin TE, Sampson HA, Camargo CA Jr, et al. Persistent, refractory, and biphasic anaphylaxis: a multidisciplinary Delphi study. *J Allergy Clin Immunol* 2020;146(5):1089–96.
25. Lee S, Peterson A, Lohse CM, et al. Further evaluation of factors that may predict biphasic reactions in emergency department anaphylaxis patients. *J Allergy Clin Immunol Pract* 2017;5(5):1295–301.
26. Golden DBK. Anaphylaxis to insect stings. *Immunol Allergy Clin North Am* 2015;35(2):287–302.
27. Umasunthar T, Leonardi-Bee J, Hodes M, et al. Incidence of fatal food anaphylaxis in people with food allergy: a systematic review and meta-analysis. *Clin Exp Allergy* 2013;43(12):1333–41.