

Anaphylaxis

Epidemiology and Differential Diagnosis



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KEYWORDS

• Anaphylaxis • Epidemiology • Differential Diagnosis

KEY POINTS

- Allergic reactions and anaphylaxis occur on a severity continuum from mild and self-limited to potentially life-threatening or fatal reactions.
- The most common causes of anaphylaxis are food, medications, and stinging insects.
- Rates of anaphylaxis-related emergency department visits and hospitalizations are increasing though fatal anaphylaxis is rare.

INTRODUCTION

Anaphylaxis is a potentially life-threatening allergic reaction. Since its initial description by Charles Richet and Paul Portier in 1902,¹ our understanding of anaphylaxis has grown in terms of its epidemiology and underlying causes.

ANAPHYLAXIS EPIDEMIOLOGY

The overall global incidence of anaphylaxis is reported to be between 50 and 112 episodes per 100,000 person-years² and the global incidence among children has been estimated to range from 1 to 761 per 100,000 person-years.³ The lifetime prevalence of anaphylaxis ranges from 0.3% to 5.1%.^{2,4} Data from Europe reported that more than a quarter of anaphylaxis cases occurred in those younger than 18 years of age.⁵

Time Trends

In the United States (US), a retrospective study⁶ based on administrative claims data found that emergency department (ED) visits for anaphylaxis increased by 101% between 2005 and 2014. During that same time frame, hospitalizations for anaphylaxis in

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the US increased by 37.6%.⁷ This mirrors global trends whereby increasing anaphylaxis-related hospitalizations have been reported in Europe,^{8,9} the United Kingdom (UK),¹⁰ and Australia.¹¹ Hospital admission rates differ by country with the highest rates in Australia and lowest rates in the US and Spain. In the US, less than 20% of anaphylaxis-related ED visits are admitted (observation or hospital ward).⁷ This is likely due to differences in admission thresholds between countries and the emergence of observation units, particularly in the US, which may not be coded as an admission.¹²

Despite increases in anaphylaxis hospitalizations, anaphylaxis fatalities in the US have been low and stable at about 0.63 to 0.75 per million adults per year. Overall, anaphylaxis-related fatalities account for an estimated 1% of hospitalizations and 0.1% of ED visits for anaphylaxis.¹³ The top 3 causes of fatal anaphylaxis in adults are medications (38%–58.8%),^{11,14} insect venom (15.2%–18%),^{11,14} and foods (6.7%).^{11,14} African American ethnicity and older age have been associated with fatal anaphylaxis, with fatal venom-related anaphylaxis more common in males and Caucasians.¹³

Common Triggers

Food is the most common trigger for anaphylaxis-related hospitalizations and highest in the pediatric population (age <18 years). The most common specific food trigger varies by age group with cow's milk more common in infants, peanuts in children, and shellfish and tree nuts in young adults and adults.¹⁵ In the US, ED visits for food-induced anaphylaxis increased by 214% ($P < .001$) from 2005 to 2014 with the highest rates reported in infants and toddlers (age 0–2 years).⁶ This supports other studies published in Spain⁹ and Canada¹⁶ whereby rates of anaphylaxis in children ages 0 to 4 years were 3 times greater than those among older age groups. Pediatric patients represent a vulnerable patient population as the diagnosis of food induced anaphylaxis in infants and children can be very challenging. Younger patients also may not have a prior diagnosis of food allergy and may present either with a subtle or delayed clinical presentation. Consequently, caregivers and health care providers must maintain a high level of suspicion when evaluating pediatric patients for reactions in the context of a food exposure.¹⁷

Medications are another common trigger for anaphylaxis. Adverse drug reactions occur in up to 10% of the general population and of those 10% are drug hypersensitivity reactions.¹⁸ The most common drug triggers in the US are antibiotics (penicillin, cephalosporins, and sulfonamides), nonsteroidal anti-inflammatory drugs (NSAIDs), biologics, and immunomodulators.^{19–21} Medications are the most common cause of fatal anaphylaxis in the US¹⁴ and elsewhere including Brazil, New Zealand, Australia, and the UK. In contrast to other allergic triggers, rates of fatal medication-induced anaphylaxis are increasing.¹⁴ Data from the UK fatal anaphylaxis registry reported that many of those with fatal drug anaphylaxis had no prior indication of drug allergy suggesting that the first reaction can be fatal.^{22,23}

Stinging insects are a common trigger in both pediatric and adult patient populations. Systemic reactions to insect stings may affect up to 0.8% of children and 3% of adults with at least 40 fatal stings per year nationally.²⁴ The most common insect triggers include hymenopterans (yellow jacket, hornet, wasp, honeybee and imported fire ant). Venom specific triggers differ by region with wasp more common in Austria, Germany, and central Europe⁵ whereas honeybee is more common in South Korea.²⁵ The incidence of insect allergy has increased in some areas and decreased in others, which experts have attributed to multiple factors including insect migration, climate change, and the encroachment of humans into new habitats.²⁶ Although insect allergy

is more common in young adults, fatal anaphylaxis due to insect stings is more likely to occur in adults older than 45 years of age, likely related to comorbidities and impaired compensatory mechanisms.²⁷ Similar to drug induced reactions, published data from the UK fatal anaphylaxis registry^{22,23} suggest that the initial venom-induced anaphylactic reaction can be fatal.

Differential Diagnosis

Anaphylaxis phenotypes

Castells²⁸ published a new classification scheme for anaphylaxis based on phenotypic presentations and on underlying endotypes. The phenotypes are defined by clinical presentation into 4 types: (1) type I-like reactions, (2) cytokine storm-like reactions, (3) mixed reactions, and (4) complement reactions (Fig. 1). Type I-like reactions present with a spectrum of signs and symptoms including pruritus, hives, flushing, shortness of breath, vomiting, and cardiovascular collapse and may be due to both immunoglobulin E (IgE)- and non-IgE-mediated mechanisms. Typical IgE-mediated triggers include foods, medications, and Hymenoptera venoms. Non-IgE-mediated reactions may occur through mast cell mediator release via the Mas-related G protein-coupled receptor X2 (MRGPRX2), a newly described G-coupled receptor

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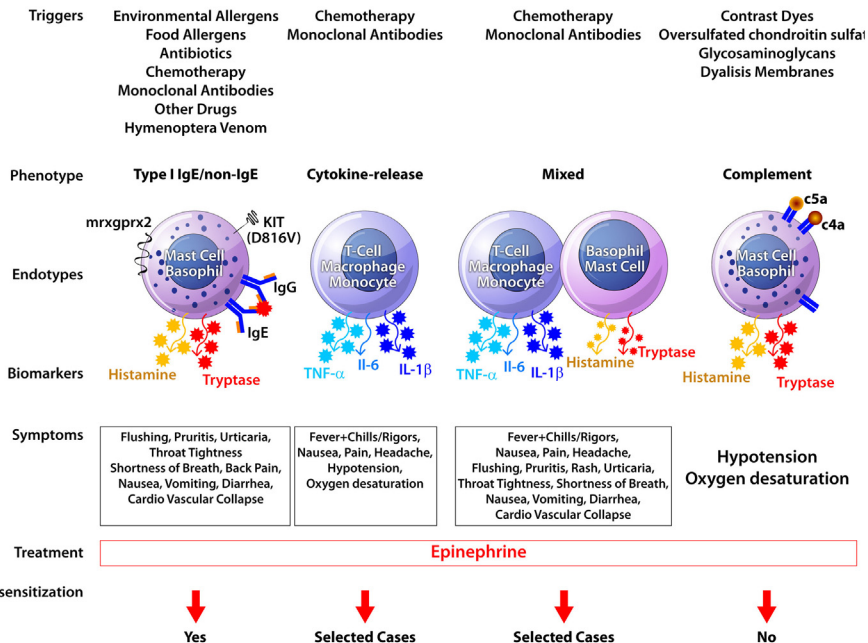


Fig. 1. Pathways of anaphylaxis. Phenotypes of anaphylaxis include type I reactions, cytokine storm-like reactions, and mixed reactions. Endotypes of anaphylaxis include IgE- and non-IgE-mediated reactions, direct mast cell and basophil activation, cytokine release, and mixed reactions. Biomarkers include tryptase, histamine, and other mast cell/basophil mediators, as well as cytokines, such as TNF- α , IL-1 β , and IL-6. Desensitization is indicated in type I reactions and selected cases of cytokine storm and mixed reactions but not in direct mast cell/basophil release. (From Castells M. Diagnosis and management of anaphylaxis in precision medicine. *J Allergy Clin Immunol.* 2017 Aug;140(2):321 to 333.)

expressed on mast cells. Drugs with tetrahydroisoquinoline (THIQ) motifs, which include quinolone antibiotics (eg, levofloxacin and ciprofloxacin) along with neuromuscular-blocking agents (eg, atracurium and rocuronium) have been shown to directly activate mast cells via the MRGPRX2 receptor. IgG-dependent pathways is another mechanism of non-IgE-mediated reactions as animal models and human observational studies have shown that IgG alone and in immune complexes can activate mast cells and contribute to anaphylactic reactions.²⁹ Rituximab and other chimeric IgG monoclonal antibodies can trigger histamine and tryptase release potentially supporting the role of IgG in anaphylactic reactions.²⁸

In contrast, cytokine storm-like reactions, the second type of anaphylaxis in the aforementioned scheme, present with fever, chills, headache, malaise and may be followed by hypotension, oxygen desaturation, and myocardial dysfunction. Severe cases may lead to disseminated intravascular coagulation and multi-organ failure. Such reactions are due to the release of proinflammatory mediators IL-1 β , IL-6, and TNF- α . Monoclonal antibodies and chemotherapy agents such as oxaliplatin are triggers for these types of reactions. Corticosteroid and COX-1 inhibitor pretreatment do not prevent severe reactions but have been used to decrease intensity. When reactions present with a combination of type 1 and cytokine storm like reactions (eg, hives, swelling, fever, chills, hypotension, and desaturations), they are labeled as mixed reactions (type 3). Monoclonal antibodies and chemotherapy agents are causes of mixed reactions.

The fourth anaphylaxis phenotype is due to direct mast cell activation as can occur with vancomycin or through complement activation by contrast dyes, oversulfated chondroitin sulfate, and glycosaminoglycans. Patients with this phenotype may present with hives, oxygen desaturation, and hypotension.

Exercise-induced anaphylaxis

In addition to foods, drugs, and Hymenoptera venom, exercise is another important trigger for anaphylaxis. Exercise-induced anaphylaxis (EIA) reportedly occurs in up to 3% of all anaphylaxis cases.³⁰ EIA is subcategorized into (1) drug-dependent exercise-induced anaphylaxis (DDEIA), (2) food-independent exercise-induced anaphylaxis (FIEIA), and (3) food-dependent exercise-induced anaphylaxis (FDEIA) with and without IgE sensitivity. In terms of its natural history, for most patients with EIA the frequency of attacks tends to stabilize (46%) or decrease (47%).³¹

In cases of FIEIA, exercise is the only trigger with the most common reported exercise activities being running, brisk walking, biking, racquet sports, intense gardening, and vigorous dancing.³⁰ In DDEIA, the combination of drug intake with exercise triggers anaphylaxis. The most common drug triggers are NSAIDs with cases of cephalosporins reported.³⁰

FDEIA is a disorder in which anaphylaxis develops when exercise takes place within a few hours of ingesting a specific food. Frequently cited food triggers in Western populations include wheat with the major protein epitope omega-5-gliadin, other grains, and nuts. In Asian populations, wheat and shellfish are most common though other foods including seeds, vegetables, fruits, meats, cow's milk, and egg have been reported.³² Whether exercise increases the absorption of the allergen³³ or lowers the activation threshold of mast cells and basophils³⁴ remains unclear, as the specific mechanism of FDEIA has not been elucidated. FDEIA is considered a postprandial event and patients are recommended to avoid exercise for to 4 to 6 hours after eating a known food trigger, to lower exercise intensity after eating, to avoid exercising in extreme temperatures, and to carry an epinephrine autoinjector when exercising.³²

Recently, the induction of anaphylaxis has been described with the combination of food ingestion and nonexercise augmenting factors. These observations have given rise to the concept of “augmentation factor-triggered food allergy,”³⁵ and highlight the importance of cofactors in facilitating anaphylaxis.^{32,36} Augmenting factors include alcohol, menstruation, acute infections, and medications specifically NSAIDs and antacids. As these factors may lower the reaction threshold and increase reaction severity, cases of anaphylaxis should be evaluated for augmenting factors as they play an important role in the development of allergic reactions.³⁶

Idiopathic anaphylaxis

When no trigger is identified, anaphylaxis is classified as idiopathic. Idiopathic anaphylaxis (IA) accounts for up to 30% to 60% of cases of anaphylaxis in adults and up to 10% of cases in children.^{37–39} IA occurs more commonly in women than in men.³⁷ Those with IA have a high frequency of atopy as 48% of IA patients have food allergy, allergic rhinitis, or other atopic condition.⁴⁰ It is a diagnosis of exclusion as systemic mastocytosis and other mast cell disorders need to be ruled out. In addition, over the last decade, sensitivity to novel allergens such as the oligosaccharide galactose- α -(1,3)-galactose (α -gal) have reclassified previous cases of IA.⁴¹

α -Gal anaphylaxis

Sensitization to α -gal has been classically associated with 2 distinct presentations: (1) immediate hypersensitivity reaction to cetuximab and (2) delayed anaphylaxis to red meat (noncatarrhine mammalian meat). The unique delayed reaction is thought to be due to the digestive processes required to expose the carbohydrate moiety.⁴² Cases of α -gal have been reported in the US and worldwide including Australia, Japan, Africa, and Europe.⁴³ Sensitization to α -gal occurs via tick bites with the lone star tick (*Amblyomma americanum*) being the relevant tick species in the US (Fig. 2).⁴³ In a single center retrospective study, α -gal was the most common cause of anaphylaxis. On a follow-up report from the same center, the percentage of IA cases decreased from 59% in their previous report to 35%, which the authors attributed to the recognition of α -gal cases.^{39,41} Additional research is needed to identify additional novel allergens to further clarify cases of IA.

Non-allergic mimics of anaphylaxis

The differential diagnosis of anaphylaxis is broad and includes flushing syndromes (pheochromocytoma, carcinoid tumor, medullary carcinoma of the thyroid, and vaso-vagal reactions), restaurant syndromes (scombroidosis and monosodium glutamate ingestion reactions), and nonorganic disease (Munchausen stridor, vocal cord dysfunction, and panic attack).¹⁵ A more comprehensive list of nonallergic differential diagnoses is listed in Box 1.

Diagnostic Challenges

Anaphylaxis is underrecognized and underdiagnosed.^{44,45} Anaphylaxis is frequently missed in patients seen in the ED, undergoing anesthesia and surgery, and those treated with biologic agents such as monoclonal antibodies and chemotherapy.²⁸ This is likely due to the myriad of associated diagnostic challenges and the spontaneous recovery of the majority of affected individuals. Anaphylaxis lacks a clinically useful definition and a reliable, diagnostic biomarker. There exists a disconnect in how anaphylaxis has been defined traditionally based on IgE, mast cells, and basophils and how the diagnosis of anaphylaxis is applied clinically. In fact, a round table meeting⁴⁶ of ED providers concluded, “the traditional mechanistic definition of anaphylaxis is not useful.”

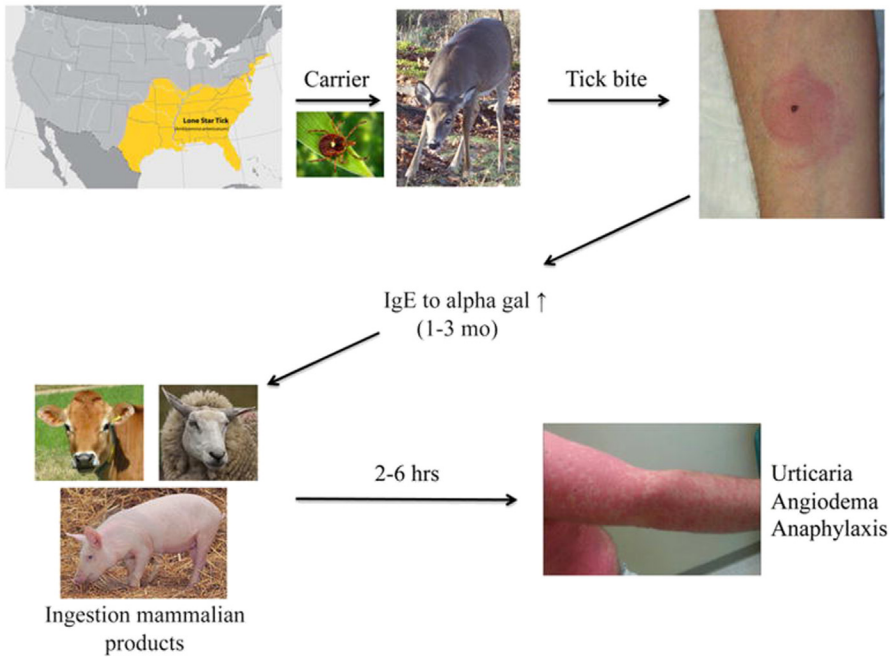


Fig. 2. Summary of α -Gal sensitization leading to clinical symptoms of red meat allergy. The southeastern section of the US is where most of the reactions to meat derived from non-primate mammals (eg, beef, lamb, or pork) have been reported. This region overlaps with the distribution of the Lone Star tick, *Amblyomma americanum*. The current hypothesis is that people are bitten by Lone Star ticks carried by deer into rural and urban areas. Following a period of time, IgE to α -Gal develops. Once specific-IgE to α -Gal reaches sufficient levels, ingestion of red meat can trigger reactions. (Adapted from Steinke JW, Platts-Mills TA, Commins SP. The alpha-gal story: lessons learned from connecting the dots. *J Allergy Clin Immunol*. 2015 Mar;135(3):589-96; quiz 597.)

In addition, although there have been numerous national and international guidelines published, the lack of consensus between these guidelines compounds current challenges. For example, a food-induced reaction that results in persistent vomiting and dyspnea (without bronchospasm) would constitute anaphylaxis under NIAID/FAAN criteria.⁴⁷ However, under guidelines published in the UK⁴⁸ and Australia,⁴⁹ these presenting symptoms would not meet anaphylaxis criteria given the absence of mucocutaneous manifestations.⁵⁰ Refinements to the NIAID/FAAN clinical criteria were recently proposed by the WAO Anaphylaxis Committee⁵¹ but the impact on clinical management is unknown.

In addition, beyond establishing consensus guidelines, efforts to disseminate these recommendations to address knowledge, and practice gaps are needed. In a cross-sectional survey of over 3000 paramedics in the US, 98% correctly identified a "classic case" in which a patient presented with urticaria, itching, and angioedema after exposure to penicillin. However, only 2.9% were able to identify an atypical case without the usual skin findings or a known allergen exposure.

A lack of available point of care testing represents another diagnostic challenge. Although anaphylaxis is a clinical diagnosis, the use of biomarkers may support the diagnosis and assist clinicians in differentiating anaphylaxis from potential mimics.

Box 1**Differential diagnosis of anaphylaxis**

Neurologic/autonomic dysregulation

1. Vasovagal and vasodepressor reactions
2. Postural orthostatic tachycardia syndrome
3. Seizure
4. CVA

Cardiovascular

1. Cardiogenic shock
2. Hemorrhagic shock
3. Vasodilatory/distributive/endotoxic shock
4. Capillary leak syndrome (hypovolemic shock)
5. Pulmonary embolus

Endocrine/flushing

1. Carcinoid
2. Pheochromocytoma
3. VIP-secreting tumors
4. Thyroid medullary carcinoma
5. Menopause (flushing, hot flashes)
6. Hypoglycemia

Iatrogenic/drugs

1. Vancomycin (Red Man syndrome)
2. Niacin (flushing)
3. General and spinal anesthetics (hypotension)

Toxic

1. "Restaurant syndromes"
 - a. Scombroidosis
 - b. MSG
2. Alcohol
3. Sulfites

Hematologic/malignant

1. Systemic mastocytosis
2. Urticaria pigmentosa
3. Basophil leukemia
4. Acute promyelocytic leukemia with tretinoin treatment

Immunologic

1. Bradykinin-mediated angioedema

Infection

1. Hydatid cyst (*Echinococcus granulosus*)
2. Sepsis/septic shock

Psychosomatic/functional disorders

1. Panic attack
2. Factitious anaphylaxis
 - a. Munchausen stridor
3. Undifferentiated somatoform anaphylaxis
4. Vocal cord dysfunction

Abbreviations: C1, complement 1; C4, complement 4; CBC, complete blood count; CVA, cerebrovascular accident; EtOH, ethanol; FSH, follicle-stimulating hormone; 5-HIAA, urine 5-hydroxy indole acetic acid; LH, luteinizing hormone; MSG, monosodium glutamate; RHC, right heart catheterization; TTE, transthoracic echocardiogram; VIP, vasoactive intestinal peptide.

Adapted from LoVerde D, Iweala OI, Eginli A, Krishnaswamy G. Anaphylaxis. Chest. 2018 Feb;153(2):528-543.

The main biomarker currently available is serum tryptase.²⁰ Serum tryptase is increased 30 minutes following the onset of a reaction, peaks 1 to 2 hours after reaction onset, and remains elevated up to 6 to 8 hours.²⁸ However, although tryptase is recommended by current guidelines, it is not useful for ED providers as results are typically not available in time to guide clinical decision-making. In addition, although its positive predictive value is high (93%), total serum tryptase has a low negative predictive value.⁵² Moreover, tryptase is often not elevated in cases of food-induced anaphylaxis. Additional biomarkers, such as platelet activating factor, chymase, chemokine ligand-2, and carboxypeptidase A3, are being studied but are difficult to measure.⁵³ Future studies are needed to identify additional candidate biomarkers along with examining the sensitivity and specificity of using combinations of biomarkers. In addition, the barrier of obtaining timely biomarker results to facilitate clinical decision making needs to be addressed.

New Advances in Anaphylaxis

Updated anaphylaxis treatment recommendations were published in 2020. Based on a recently updated Joint Task Force on Practice Parameters (JTFPP),¹⁹ routine use of postevent glucocorticoids and antihistamines is no longer recommended as an intervention to prevent biphasic anaphylaxis. The benefit of glucocorticoids and antihistamines in the acute management of anaphylaxis and in the prevention of biphasic anaphylaxis has not been established.^{54,55} In addition, studies have raised concerns

Box 2

Clinical criteria for diagnosing persistent, refractory, and biphasic anaphylaxis

Persistent anaphylaxis is highly likely when the following criterion is fulfilled:^a

1. Presence of symptoms/examination findings that fulfil the 2006 NIAID/FAAN anaphylaxis criteria that persist for at least 4 h¹

Refractory anaphylaxis is highly likely when both of the following 2 criteria are fulfilled:^b

1. Presence of anaphylaxis following appropriate epinephrine dosing and symptom-directed medical management (eg, IV fluid bolus for hypotension).
2. The initial reaction must be treated with 3 or more appropriate doses of epinephrine (or initiation of an IV epinephrine infusion).^c

Biphasic anaphylaxis is highly likely when all of the following 4 criteria are fulfilled:^d

1. New/recurrent symptoms/examination findings must fulfil the 2006 NIAID/FAAN anaphylaxis criteria.¹
2. Initial symptoms/examination findings must completely resolve before the onset of new/recurrent symptoms/examination findings.
3. There cannot be allergen reexposure before the onset of new/recurrent symptoms/examination findings.
4. New/recurrent symptoms/examination findings must occur within 1–48 h from complete resolution of initial symptoms/examination findings.

^a The diagnosis of persistent anaphylaxis is independent of the management of the initial reaction.

^b Refractory anaphylaxis is not dependent on the duration of symptoms/examination findings.

^c Appropriate epinephrine dosing: 0.01 mg/kg IM epinephrine, maximum single dose 0.5 mg. Also includes manufacturer recommended dosing for epinephrine auto-injectors.

^d The diagnosis of biphasic anaphylaxis is independent of the management of the initial reaction.

From 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.

Severity grading system for acute allergic reactions		
Grading system application is INDEPENDENT of whether reactions fulfill NIAID/FAAN anaphylaxis diagnostic criteria ^a (e.g. a reaction can be either Grade 5 anaphylaxis or a Grade 5 non-anaphylactic reaction)		
	Severity grades ^b	Clinical criteria (sub-grading system)
Life threatening allergic reactions ↑ Mild allergic reactions	5	ANY Severe: Cardiovascular, Neurologic, Respiratory
	4	ANY Moderate: Cardiovascular, Neurologic, Respiratory OR Severe: Mucosal/angioedema
	3	ANY Mild: Cardiovascular, Neurologic, Respiratory
	2	2 or more Mild, ANY Moderate: Skin, Gastrointestinal, Mucosal/angioedema
	1	ANY Mild: Skin, Gastrointestinal, Mucosal/angioedema
Terms: Symptoms: patient and/or family reported symptoms, not observed by clinicians; Signs: clinical and/or examination findings; Infants: signs and symptoms of allergic reactions in infants and young children may overlap with normal behavior. Mild/moderate respiratory, neurologic or CV symptoms may represent increased reaction severity in infants and young children. Definitions Hypotension: Pediatric: systolic BP < 5th percentile for age or < 2 standard deviations below normal for age or systolic BP < 70 mm Hg from 1 month to 1 year, < (70 mm Hg + [2 X age]) from 1 to 10 years, and < 90 mm Hg from 11 to 17 years. Hypotension is a late phase sign in young children; consider use of HR and other CV symptoms in infants. Do not delay management of anaphylaxis for acquisition of BP. Adult: estimated or calculated mean arterial pressure (MAP=1/3[systolic BP]+2/3[diastolic BP]) < 65; or systolic BP < 90 mm Hg or > 30% decrease from baseline Anaphylactic shock: anaphylaxis with an IV vasopressor infusion requirement to maintain a MAP ≥ 65 mmHg or systolic BP ≥ 90 mm Hg among adults, and age appropriate BPs among children (see pediatric definitions of hypotension above) Increased work of breathing (WOB): retractions, use of accessory muscles, nasal flaring or grunting (infants), age defined tachypnea that is not brief or self-resolved Hypoxemia: SpO ₂ ≤ 92% on room air Respiratory failure: impaired oxygenation or ventilation requiring use of non-invasive and/or invasive ventilatory support (bag mask ventilation, high flow nasal cannula, continuous positive airway pressure, bi-level positive airway pressure, mechanical ventilation, extracorporeal membrane oxygenation)		
Cardiovascular^c MILD: Symptoms - weak, dizzy, pre-syncope, palpitations, blurred vision; Infants - tachycardia not related to other causes such as crying, discomfort, or medications MODERATE: hypotension, syncope (collapse); Infants - mottling, cyanosis SEVERE: anaphylactic shock, cardiac arrest; Infants - hypotension Neurologic^d MILD: Symptoms - confusion, drowsy, sense of impending doom; Infants - persistent and unexplained irritability, inconsolability, crying, or decreased activity MODERATE: GCS (Glasgow Coma Scale; https://www.mdcalc.com/glasgow-coma-scale-score-gcs) 13-14; Infants - lethargic SEVERE: GCS <13, seizure; Infants - new onset hypotonia Respiratory General MILD: Symptoms - chest tightness, dyspnea; Signs - new onset cough MODERATE: new onset persistent cough, increased WOB, hypoxemia SEVERE: respiratory failure Laryngeal MILD: Symptoms - throat tightness or discomfort; Signs - voice change; Infants - barking or croup like cough, hoarse cry MODERATE: stridor w/o increased WOB SEVERE: stridor with increased WOB (partial or complete upper airway obstruction) Lower airway MILD: wheezing w/o increased WOB MODERATE: wheezing with increased WOB SEVERE: bronchospasm with minimal or no air movement on auscultation AND increased WOB Mucosal/angioedema (see Figure E1 in the online repository for example images of mucosal/angioedema severity) MILD: Symptoms - mouth tingling, itchy mouth or throat, metallic taste; Signs - facial swelling, conjunctival injection, chemosis, nasal congestion, rhinorrhea, throat clearing, lip swelling, mild tongue, soft palate, and/or uvula swelling (anatomical landmarks preserved); Infants - tongue thrusting or pulling, repetitive lip, ear or eye rubbing MODERATE: drooling, moderate tongue, soft palate, and/or uvula swelling (anatomical landmarks obscured); Infants - marked increase in drooling SEVERE: severe tongue, soft palate, and/or uvula swelling (complete loss of anatomical landmarks) Skin Pruritus MILD: Symptoms - pruritus, skin discomfort; Signs - occasional scratching, localized scratching or excoriations (< 50% body surface area [BSA]) MODERATE: continuous scratching, generalized scratching or excoriations (≥ 50% BSA) Urticaria, rash MILD: localized urticaria (< 50% BSA), localized erythema (< 50% BSA) MODERATE: generalized urticaria (≥ 50% BSA), flushing, generalized erythema (≥ 50% BSA) Gastrointestinal MILD: Symptoms - nausea, abdominal pain ^e ; Signs - 1-2 episodes of emesis or diarrhea; Infants - new onset spitting up, hiccups, or back arching MODERATE: Symptoms - frequent or continuous nausea or abdominal pain, distressed due to GI symptoms; Signs - ≥3 episodes of emesis or diarrhea or 2 of each		

Fig. 3. Severity grading system for acute allergic reactions. ^aFor patients with multiple symptoms, reaction severity is based on the most severe symptom; symptoms that constitute more severe grades always supersede symptoms from less severe grades. The grading system can be used to assign reaction severity at any time during the course of reactions; reactions may progress rapidly (within minutes) from one severity grade to another. The grading system does not dictate management decisions; reactions of any severity grade may require treatment with epinephrine. ^bPatients with severe cardiovascular and/or neurologic involvement may have urinary or stool incontinence. However, the significance of incontinence as an isolated symptom is unclear, and it is therefore not included as a symptom in the subgrading system. ^cAbdominal pain may also result from uterine cramping. (From Dribin TE, Schnadower D, Spergel JM, et al. Severity grading system for acute allergic reactions: A multidisciplinary Delphi study [published online ahead of print, 2021 Jan 19]. J Allergy Clin Immunol. 2021;S0091-6749(21)00047-6.)

regarding the harmful effects of glucocorticoids.⁵⁶ The most recent European Academy of Allergy and Clinical Immunology guidelines⁵⁷ have moved antihistamines from second line to a third line measure to treat cutaneous anaphylaxis symptoms. The role antihistamines and glucocorticoids in the acute management of anaphylaxis will need to be further clarified.¹²

In addition, the JTFPP also recommends an extended observation for those with risk factors for biphasic anaphylaxis or increased risk of anaphylaxis fatality (eg, resolved severe anaphylaxis, those requiring more than one dose of epinephrine, cardiovascular comorbidity, lack of access to epinephrine or emergency medical services, or poor self-management skills). Data are lacking regarding the optimal observation duration that is cost-effective.

To address the use of inconsistent definitions for anaphylaxis outcomes, a multidisciplinary panel proposed consensus definitions for persistent, refractory, and biphasic anaphylaxis as well as a severity grading system for acute allergic reactions^{58,59} (Box 2 and Fig. 3). Validation with subsequent dissemination and application of these definitions and grading scale will aid in standardizing the terminology used to describe anaphylaxis outcomes and severity. Consistent diagnosis will advance anaphylaxis clinical care and outcome research.

SUMMARY

Since its initial description 120 years ago, our understanding of anaphylaxis has grown. The discovery of novel allergens such as α -gal and recently updated guidelines exemplify the progress made in improving our understanding and management of anaphylaxis. However, as anaphylaxis continues to be underrecognized and underdiagnosed, it is likely that anaphylaxis is far more common than previously and currently reported. Efforts to address deficiencies such as the need for biomarkers and establishing international consensus definitions and guidelines are necessary to improve the diagnosis and management of anaphylaxis.

CLINICS CARE POINTS

- Rates of anaphylaxis-related ED visits and hospitalizations are increasing.
- Triggers for anaphylaxis include food, medications, Hymenoptera, exercise, and a novel allergen α -gal.
- Recognition of anaphylaxis endotypes provides insight into underlying mechanisms responsible for anaphylaxis phenotypes.
- The diagnosis of anaphylaxis is challenging due to the lack of a universally accepted definition, lack of consensus between published guidelines, and lack of available point of care testing.
- Recent practice guidelines have recommended against the routine use of systemic corticosteroids and antihistamines to prevent biphasic anaphylaxis and have recommended an extended observation for those with increased risk of a biphasic reaction or anaphylaxis fatality.

DISCLOSURE

R.L. Campbell is an author for UpToDate and a consultant for Bryn Pharma. All other authors declare no conflicts of interest.

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