



CME Review

Knowledge gaps in the diagnosis and management of anaphylaxis



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Key Messages

- Although the National Institute of Allergy and Infectious Disease and World Allergy Organization anaphylaxis criteria are similar, they have significant differences, resulting in 6 combinations of symptoms that would fulfill one but not both definitions of anaphylaxis.
- Many of the signs and symptoms in the National Institute of Allergy and Infectious Disease and World Allergy Organization definitions of anaphylaxis cannot be determined in infants and minimally verbal populations or for perioperative anaphylaxis, and these remain crucial knowledge gaps to address as our understanding of anaphylaxis evolves.
- There are multiple anaphylaxis severity grading systems that exist, each with strengths and weaknesses, but no system has proven to be superior for all uses and contexts, many lack validation, and a harmonization of these systems is needed.
- There are few reliable biomarkers for diagnosing anaphylaxis that are reliable across all reaction triggers.
- There is considerable variation in defining biphasic anaphylaxis, post-anaphylaxis observation time or criteria for hospitalization, the risk of concomitant beta-blocker or ACE inhibitor use, and risk factors for biphasic anaphylaxis.
- There are poor data to substantiate that many frequently recommended current anaphylaxis policies are necessary, such as when caregivers should be instructed to use epinephrine, the role of activating emergency services after administering a single dose of epinephrine, the optimal number of epinephrine units to prescribe and carry, the role of antihistamine and corticosteroids in managing anaphylaxis, and the degree to which epinephrine use truly reduces poor outcomes and prevents fatality.

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ABSTRACT

Knowledge gaps in the diagnosis and treatment of anaphylaxis impede the clinician's ability to effectively manage patients with anaphylaxis. This review will emphasize the lack of a global consensus on defining and determining the severity of anaphylaxis; the need for validating biomarkers used for diagnosing anaphylaxis; and data collection deficiencies. Perioperative anaphylaxis has a wide differential diagnosis, often requires treatment beyond epinephrine, and poses a challenge for the clinician in identifying the responsible trigger(s) and in preventing future reactions. Consensus-derived definitions and determination of risk factors for biphasic, refractory, and persistent anaphylaxis are needed, recognizing that these often affect the emergency department observation time after recovery from initial anaphylaxis. Knowledge gaps exist in the use of epinephrine, including route of administration, dosage, needle length, and ideal timing for administration. Consensus is needed on when and how many epinephrine autoinjectors to prescribe and how to prevent patient underuse and accidental injury. The role of antihistamines and corticosteroids in the prevention and treatment of anaphylaxis requires consensus and additional research. A consensus-derived algorithm for management of idiopathic anaphylaxis is needed. The role of beta-blockers and angiotensin-converting enzyme inhibitors in the incidence, severity, and treatment of anaphylaxis remains unanswered. Rapid recognition and treatment of anaphylaxis in the community needs improvement. The article will conclude with exploring the recommended components of both a patient-specific and generic anaphylaxis emergency plan, including when to activate emergency medical services, all of which are paramount to improving patient outcomes.

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- Identify the differences among international anaphylaxis diagnostic criteria, as well as key facets of epinephrine pharmacokinetics.
- Describe risk factors for worsening anaphylaxis among patients on beta-blockers and angiotensin converting enzyme inhibitors.

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Introduction

It is estimated that 1% to 3% of the global population has a lifetime risk for anaphylaxis.^{1–3} In the past 10 years, new research and the updated clinical guidelines on anaphylaxis have improved both the diagnosis and treatment of this life-threatening disorder; however, many knowledge gaps remain.⁴ Owing to ethical concerns, randomized controlled trials (RCTs) cannot be conducted to answer many important questions on anaphylaxis, especially those involving treatment; therefore, the level of certainty in the evidence is usually low to very low. The scope of this review will be limited to the key knowledge gaps in evidence-based and consensus-derived knowledge gaps in the clinical diagnosis and acute management of anaphylaxis. Knowledge gaps present among specific stakeholders, for example, primary care physicians, patients, caretakers, or the public at large, will not be addressed. Although knowledge gaps are present in other aspects of anaphylaxis, for example, epidemiology, pathophysiology, risk factors, and prevention, these areas will be addressed only as they directly affect the diagnosis and treatment of anaphylaxis. Mast cell disorders are discussed only in the context of the differential diagnosis or for their impact on anaphylaxis. Many of the knowledge gaps discussed herein have also been identified by experts in recent guidelines, systematic reviews, and international surveys.^{4–9} Although high certainty of evidence is rarely present for anaphylaxis management, in identifying areas on which our current diagnosis and treatment of anaphylaxis is based, low certainty of evidence is

also valuable, because these areas inform the clinician where to use shared decision-making and to identify questions for future research.

The key knowledge gaps in diagnosis and treatment and the need for consensus and further research are listed in [Table 1](#) and [Table 2](#), respectively. The background and implications for these gaps are discussed in this paper, with each subheading referencing the respective gaps by table and item number.

Methods

A narrative review was completed using a literature search of PubMed, Google Scholar, and the Cochrane Database of Systematic Reviews of English-language articles published between January 1, 2012, and March 12, 2023. For historical perspective, the time frame was expanded to 1977 for select articles. Systematic reviews and randomized trials provide the highest level of evidence; however, articles on anaphylaxis are observational, crossover, case series, surveys, or expert opinion. Although a systematic review provides a more comprehensive and less biased review of the evidence, this was beyond the scope and resources of this review article.¹⁰ Key search words included anaphylaxis, anaphylaxis definition, anaphylaxis emergency plan (AEP), corticosteroids, antihistamine(s), epinephrine, adrenaline, epinephrine autoinjector (EAI), perioperative anaphylaxis (POA), mast cell, mastocytosis, tryptase, beta-blocker (BB), angiotensin, insect venom hypersensitivity, allergy immunotherapy, and food allergy.

Table 1
Knowledge Gaps in the Diagnosis of Anaphylaxis

Number	Current needs or lack of data to determine the following:	Section of manuscript discussed
1	A global definition and set of clinical criteria for diagnosing anaphylaxis	Gaps in diagnosis of anaphylaxis
2	Determine whether a separate set of clinical criteria for diagnosing anaphylaxis in infants and non- or minimally verbal populations and perioperative patients improves outcomes	Gaps in diagnosis of anaphylaxis
3	The need for the anaphylaxis definition and criteria to use patient observable symptoms and terminology without requiring physiological measurements or medical examination	Gaps in diagnosis of anaphylaxis
4	Point-of-care combination of symptoms to inform when to administer epinephrine during a severe allergic reaction and/or evolving anaphylaxis	Gaps in diagnosis of anaphylaxis
5	The validity of the use of epinephrine and the observed clinical response as a surrogate marker for anaphylaxis	Gaps in diagnosis of anaphylaxis
6	A validated global severity scoring system for anaphylaxis	Gaps in diagnosis of anaphylaxis
7	The best biomarker and validated thresholds to establish or confirm the diagnosis of anaphylaxis and predict the severity of future reactions	Biomarkers: diagnosing anaphylaxis
8	Validation of screening and confirmatory diagnostic testing for diagnosing H α T and mastocytosis in patients with IA	Biomarkers: diagnosing anaphylaxis
9	Validation of threshold level of bST before screening for H α T in patients with IA	Biomarkers: diagnosing anaphylaxis
10	Validation of using TSAB1 copy number in conjunction with bST to determine the need for a clonal mastocytosis workup in patients with IA	Biomarkers: diagnosing anaphylaxis
11	Validation of the bST value for which a high-sensitivity peripheral blood DK16VKIT should be obtained in patients with anaphylaxis	Biomarkers: diagnosing anaphylaxis
12	Validation of screening all venom hypersensitivity patients for mastocytosis	Biomarkers: diagnosing anaphylaxis
13	Improved data collection (from hospital, other medical facilities, community) for occurrence of all anaphylaxis/severe allergic reactions including the location, trigger, timing of symptom onset and evolution, cofactors, comorbidities, initial and subsequent treatment by location, and outcomes.	Anaphylaxis data collection
14	Clinical algorithm for use at point of care to diagnosis of POA	Perioperative anaphylaxis: diagnosis and treatment
15	Positive and negative likelihood ratios for diagnostic skin testing and challenge for pharmacologic and nonpharmacologic agents potentially responsible for POA	Perioperative anaphylaxis: diagnosis and treatment
16	Optimal timing for skin testing and challenge after POA	Perioperative anaphylaxis: diagnosis and treatment
17	The cross-reactivity of alternative, chemically similar pharmacologic agents for use during surgery	Perioperative anaphylaxis: diagnosis and treatment
18	Method for accessing all pharmacologic agents used during surgery and alternative agents for future use	Perioperative anaphylaxis: diagnosis and treatment
19	Validation of high-sensitivity in vitro sIgE and BAT to identify agents responsible for POA	Perioperative anaphylaxis: diagnosis and treatment
20	Predictive value of both positive- and negative-graded challenges for agents potentially responsible for POA	Perioperative anaphylaxis: diagnosis and treatment
21	Definition of biphasic refractory and persistent anaphylactic reactions	Biphasic, refractory, and persistent anaphylaxis and ED observation time
22	Determination whether there should be a requirement for epinephrine administration during initial anaphylaxis before diagnosing biphasic anaphylaxis	Biphasic, refractory, and persistent anaphylaxis and ED observation time
23	Determination of what treatment is required before fulfilling the definition of refractory and persistent anaphylaxis	Biphasic, refractory, and persistent anaphylaxis and ED observation time
24	Validation of risk factors for biphasic anaphylaxis	Biphasic, refractory, and persistent anaphylaxis and ED observation time

Abbreviations: BAT, basophil activation test; bST, baseline serum tryptase; ED, emergency department; H α T, hereditary alpha tryptasemia; IA, idiopathic anaphylaxis; POA, perioperative anaphylaxis; sIgE, specific immunoglobulin E; TSAB1; tryptase alpha/beta 1.

Table 2
Knowledge Gaps in the Management of Anaphylaxis

Number	Current needs or lack of data to determine the following:	Section of manuscript discussed
1	Validation of the use of vasopressin and methylene blue for POA refractory to anaphylaxis	Perioperative anaphylaxis: diagnosis and treatment
2	Validation of the use of albumin and colloids for hypotension refractory to crystalloid fluid replacement during POA	Perioperative anaphylaxis: diagnosis and treatment
3	Benefit of premedication for repeat surgery with the same or an alternative perioperative agent(s) with and without diagnostic testing/challenge	Perioperative anaphylaxis: diagnosis and treatment
4	Treatment algorithm for selecting preferred perioperative agents for future surgery after POA, with and without diagnostic testing/challenge	Perioperative anaphylaxis: diagnosis and treatment
5	Algorithm for determining an individual patient's ED observation time based on a risk/benefit assessment	Biphasic, refractory, and persistent anaphylaxis and ED observation time
6	Time(max) and concentration(max) for IM and SC epinephrine with site confirmed by ultrasound	Epinephrine: use, route of administration, dosage, needle length, and timing
7	Guidelines for IV vs IM epinephrine using risk/benefit assessment	Epinephrine: use, route of administration, dosage, needle length, and timing
8	Global consensus on most ideal dose and needle length of EAI for anaphylaxis in infants, children, and adults	Epinephrine: use, route of administration, dosage, needle length, and timing
9	Risk of IO injection in infant based on needle length and adverse events if IO is given	Epinephrine: use, route of administration, dosage, needle length, and timing
10	Point-of-care, patient-friendly guide for when to administer epinephrine during a suspected allergic reaction. Needed for both a patient-specific and generic AEP for epinephrine use.	Epinephrine: use, route of administration, dosage, needle length, and timing
11	Risk stratification decision aids for when, for example, considering trigger, cofactors, comorbidities, and how many EAls to prescribe	Prescription of epinephrine autoinjectors: when and how many
12	Additional data on factors and circumstances that lead health care professionals and patients to administer or not administer epinephrine.	Epinephrine underuse and accidental injury with EAls
13	Validated ways to reduce the underuse of epinephrine for anaphylaxis	Epinephrine underuse and accidental injury with EAls
14	Validated ways to prevent accidental injury from EAls	Epinephrine underuse and accidental injury with EAls
15	Role of H ₁ and H ₂ AH and CS in the prevention of anaphylaxis, for example, allergen immunotherapy, radioccontrast agents, chemotherapy, surgery after POA, and IA	Anaphylaxis treatment: beyond epinephrine
16	Role of H ₁ and H ₂ AH and CS in the acute treatment of anaphylaxis when used with or without concurrent epinephrine.	Anaphylaxis treatment: beyond epinephrine
17	When to introduce IV fluids and oxygen in the treatment of anaphylaxis	Anaphylaxis treatment: beyond epinephrine
18	How the timing of epinephrine and supplemental treatments affect the compensatory mechanisms responsible for anaphylaxis.	Anaphylaxis treatment: beyond epinephrine
19	Evidence-based treatment algorithm for IA	Idiopathic anaphylaxis: treatment and prevention
20	Incidence of BB- and ACEI-related severe and treatment-refractory anaphylaxis in venom immunotherapy, inhalant allergen immunotherapy, drug desensitization, IA, mast cell disorders, food allergy, and drug allergy separate from the underlying cardiovascular disease	Beta-blockers and angiotensin-converting enzyme inhibitors/receptor antagonists: role in the incidence, severity, and treatment of anaphylaxis
21	The risk of selective vs nonselective BB and ACEI vs ACE receptor blockers as risk factors in anaphylaxis	Beta-blockers and angiotensin-converting enzyme inhibitors/receptor antagonists: role in the incidence, severity, and treatment of anaphylaxis
22	Determine whether BB/ACEI complicate the treatment of anaphylaxis, for example, increased doses of epinephrine and need for glucagon	Beta-blockers and angiotensin-converting enzyme inhibitors/receptor antagonists: role in the incidence, severity, and treatment of anaphylaxis
23	Evidence-based algorithm for clinical use when discussing with a patient the risk/benefit of using BB/ACEI based on patient-specific considerations	Beta-blockers and angiotensin-converting enzyme inhibitors/receptor antagonists: role in the incidence, severity, and treatment of anaphylaxis
24	Cost-effectiveness of unassigned EAI in community settings	Anaphylaxis at home and in the community
25	The content, format, delivery method, and frequency of training programs on anaphylaxis to implement in community settings to achieve best outcomes	Anaphylaxis at home and in the community
26	Role of patient-worn allergen identifiers, for example, Medi-Alert jewelry	Anaphylaxis at home and in the community
27	Role of sublingual and intranasal epinephrine for anaphylaxis treatment and their effect on outcomes	Anaphylaxis at home and in the community
28	Validated benefit of AEPs	Anaphylaxis emergency plans and anaphylaxis education
29	Need for generic and patient-specific AEP and where each should be used	Anaphylaxis emergency plans and anaphylaxis education
30	Components to include on generic and patient-specific AEPs	Anaphylaxis emergency plans and anaphylaxis education
31	Global, consensus-derived generic and patient-specific (modifiable) AEP	Anaphylaxis emergency plans and anaphylaxis education
32	Patient-friendly terminology for observable signs and symptoms of anaphylaxis	Anaphylaxis emergency plans and anaphylaxis education
33	Combination of observable signs and symptoms that indicate epinephrine should be administered	Anaphylaxis emergency plans and anaphylaxis education
34	Benefit vs risk of including AH on the AEP	Anaphylaxis emergency plans and anaphylaxis education
35	Timing and indication for AH to be administered when included on AEP	Anaphylaxis emergency plans and anaphylaxis education
36	Outcomes of early vs delayed use of epinephrine in the community setting	Anaphylaxis emergency plans and anaphylaxis education
37	Evidence-based position statement on school or classroom food bans and allergy-free tables	Anaphylaxis emergency plans and anaphylaxis education
38	Algorithm for physician/patient shared decision-making conversation of when to activate EMS after the use of an EAI by patient at home/work	Anaphylaxis emergency plans and anaphylaxis education
39	When to activate EMS for community-based anaphylaxis in public setting	Anaphylaxis emergency plans and anaphylaxis education
40	Outcomes for immediate activation of EMS vs watchful waiting after administration of epinephrine for a specific patient, for example, home setting, and for the public in a community setting	Anaphylaxis emergency plans and anaphylaxis education
41	The format, content, and frequency of clinician-provided patient-specific education on anaphylaxis	Anaphylaxis emergency plans and anaphylaxis education
42	The mechanism, format, content, and frequency of education on anaphylaxis in community settings, for example, restaurants, schools, and camps	Anaphylaxis emergency plans and anaphylaxis education
43	Patient-oriented outcomes that are most important	Conclusion
44	The modifications needed for patient education and EAP to ensure these are consistent with the individual's racial, cultural, and socioeconomic background.	Conclusion
45	Validated mechanism for assessing and addressing the psychological impact of anaphylaxis diagnosis and treatment on the patient and caretakers	Conclusion

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AEP, anaphylaxis emergency plan; AH, antihistamine; BB, beta-blocker; CS, corticosteroid; EAI, epinephrine autoinjector; ED, emergency department; EMS, emergency medical services; IA, idiopathic anaphylaxis; IM, intramuscular; IO, intraosseous; IV, intravenous; POA, perioperative anaphylaxis; SC, subcutaneous.

Gaps in Diagnosis of Anaphylaxis

Definition, Clinical Criteria, and Severity Rating of Anaphylaxis as Summarized in Table 1, items 1–6

There are many different definitions and sets of clinical criteria that researchers have used to identify when anaphylaxis is present in a specific patient. The studies cited in this manuscript, for example, have used several different definitions for acute anaphylaxis. Table 3 provides a summary of pertinent references cited in this manuscript for which the authors describe their designated definition for acute anaphylaxis. Without using a consensus-based global definition of acute clinical anaphylaxis, including agreed on meaning of the terminology used therein, we risk both under- and over-diagnosing clinical anaphylaxis and inhibit our ability to categorize the severity of anaphylaxis accurately.

At times, an anaphylaxis definition, for example, the Brighton collaboration case definition, is used in a very specific context, such as vaccine safety surveillance.¹¹ Using the 2007 Brighton collaboration case definition to provide a post hoc evaluation of coronavirus disease 2019 adverse events, up to 71% of episodes diagnosed as anaphylaxis would fail to be classified as anaphylaxis when using the National Institute of Allergy and Infectious Diseases (NIAID) and the World Allergy Organization (WAO) clinical criteria to define anaphylaxis.¹² There has recently been a revision of the Brighton collaboration definition of anaphylaxis to better align with other international definitions.¹³ However, the 2023 Brighton collaboration definition of anaphylaxis continues to emphasize objective findings, such as reduced central pulse volume and serum tryptase (ST) level, as major criteria.¹³ Such objective measures are not immediately available to assist patients, caretakers, or physicians in diagnosing acute clinical anaphylaxis, and therefore the Brighton anaphylaxis definition is of limited value for making a clinical diagnosis of anaphylaxis. A consensus-based definition is needed to identify risk factors clearly, to determine the effectiveness of prevention strategies, to develop better diagnostic markers, and to fine-tune treatment, all of which are needed to mitigate severe anaphylaxis outcomes. Both the diagnostic criteria and severity assessment need to incorporate the evolving knowledge on pathogenesis and phenotypes.

There are currently 2 leading sets of criteria for the clinical diagnosis of anaphylaxis diagnosis, the NIAID and the WAO.^{9,14} Table 4 provides a comparison of these 2 sets of criteria. Although these criteria sets are very similar, there are important differences, resulting in 6 combinations of symptoms that would fulfill one but not both definitions of anaphylaxis. As an example, a patient with laryngeal involvement, for example, hoarseness or difficulty swallowing, within 2 hours after ingestion of peanut, a food to which the patient assumes having an allergy (but without confirmation of this diagnosis), would fulfill the WAO but not the NIAID diagnosis of anaphylaxis. Similarly, the rapid onset of generalized urticaria and persistent vomiting after ingestion of a meal not containing a known allergen would be diagnosed as anaphylaxis according to the NIAID but not the WAO.

Many of the signs and symptoms in the NIAID and WAO definitions of anaphylaxis cannot be determined in infants and minimally verbal populations or for POA.^{6,15} For example, infants are more likely to present with cutaneous symptoms and subtle behavior signs, such as, pulling on ears, and fewer respiratory symptoms than older children.^{16–18} It has yet to be established whether a separate set of criteria is needed to diagnose anaphylaxis in these groups.

Further research is needed to determine whether a revised, consensus-based definition or criteria for anaphylaxis should use terminology that would allow patients to make the diagnosis without using physiological measurements, such as, hypotension, or medical examination findings, such as hypotonia or bronchospasm. It has been suggested, based on very low certainty of evidence, that the use of epinephrine and the observed clinical response to such not be used as a surrogate marker for anaphylaxis, but additional research is needed.^{6,19}

More than 30 severity grading systems have been proposed; however, none have been validated.²⁰ Many of these were for a specific trigger, for example, colloid volume substitutes, food allergy, or allergen immunotherapy.^{21,22–24,25–29,30,31} Table 5 provides a summary of representative existing severity grading systems, revealing the advantages and disadvantages of each grading system. Recently, a system of 5 severity levels that also included response to therapy was proposed for food-induced anaphylaxis.³² Only 1 grading system, one which relied on observable signs and symptoms without physiological measurements, has used a statistical analysis of the relationships among symptoms, treatment, and patient outcomes.²⁶ Furthermore, recently, an extensive review and synthesis of many severity grading systems resulted in a new 5-level severity grading system based on expert consensus, although this system has not yet been validated.³³ This new system does not rely on meeting any diagnostic criteria for anaphylaxis but requires a complete subgrading of 9 categories, for example, cardiovascular, neurologic, lower respiratory general, laryngeal, and pruritic.³³ However, in a global survey, anaphylaxis experts concluded that all scoring systems have limitations in discriminating anaphylaxis severity.³⁴ Anaphylaxis guidelines have not endorsed a single severity grading system, and global consensus on a validated severity grading system is urgently needed.

International stakeholders including medical professionals, patient advocacy groups, patients, governmental and commercial health care administrators/regulators, and coding experts should be represented in the development of an evidence-based, consensus definition and a severity scoring system for anaphylaxis.^{9,35}

Biomarkers: Diagnosing Anaphylaxis

An elevated acute ST level has been recommended by a number of guidelines to support a diagnosis of anaphylaxis.^{36–38} A normal median baseline ST³⁹ level is approximately 4.5 to 5 ng/mL in the general population.⁶ Although commercial laboratories usually suggest 11.4 ng/mL as the upper level for normal, patients without extra alleles of tryptase alpha/beta 1 (TPSAB1) usually have a baseline ST (bST) level less than 8 ng/mL.⁴⁰ However, comparing the acute ST with bST may be of more value. The diagnosis of POA⁴¹ whether because of immunoglobulin (Ig)E or non-IgE-mediated mast cell activation has often relied on an elevated ST level to support the diagnosis. An elevated acute ST level of 1.2-fold increase of bST plus 2 ng/mL has recently been validated to have a positive and a negative predictive value of 98% and 44%, respectively, for POA.^{41,42} Validation of this formula for other triggers of anaphylaxis is still needed. In patients with hereditary alpha tryptasemia (HαT), using a level above $1.68 \times$ bST for acute anaphylaxis has been found to increase specificity while maintaining sensitivity.⁴³ However, given the turnaround time for ST, this test can only be used retrospectively to support the diagnosis of anaphylaxis and not at point of care; therefore, ST has little utility for patients, families, and physicians for making a clinical diagnosis of anaphylaxis. Furthermore, acute ST is usually not helpful in food-induced anaphylaxis.³⁸

The basophil activation test (BAT) is proposed to be of benefit in diagnosing and predicting the risk of occurrence, severity, and course of anaphylaxis.⁵ With the emergence of other mast cell metabolite biomarkers that can be measured in a random urine sample, such as, β -prostaglandin-2F α , n-methyl histamine, and leukotriene E4, it is possible that these tests, once validated, could eventually be point-of-care biomarkers that could both define anaphylaxis and predict the severity of future reactions.^{38,44}

HαT is an autosomal-dominant genetic variant caused by increased copy numbers of the alpha tryptase genes encoded by the TPSAB1 locus.⁴⁵ This variant is found in 6% to 7% of the general population, is usually asymptomatic, but is reported in more than 15% of

Table 3
Acute Anaphylaxis Definitions/Criteria Used by Cited Studies

Author	Topic/objective of article	Definition/criteria used	Selection process
Wood et al, ¹ 2014	Prevalence of anaphylaxis in United States	NIAID criteria ¹⁴	Cross-sectional, random, digit-dialed phone survey followed by patient interview
Turner et al, ² 2017	Anaphylaxis mortality rate and risk factors	Usually not defined	Death certificates, anaphylaxis registries, ICD-10 codes, etc.
Pouessel et al, ³ 2018	Anaphylaxis fatality	Usually not defined	National registry, death certificates, coroner's reports
Rudders et al, ¹⁶ 2011	Infant food-induced anaphylaxis	NIAID criteria	ICD-9 codes
Samady et al, ¹⁷ 2018	Infant food-induced anaphylaxis	NIAID criteria	ICD-9/10 codes and ED record notes
Pistiner et al, ¹⁸ 2021	Infant food-induced anaphylaxis	Author derived "AAFA criteria" based upon ^{16,17,169}	Online survey of reported symptoms
Bann et al, ¹⁹ 2021	Identification and validation of anaphylaxis using electronic health data	NIAID	ICD-9 code and record review
Poachanukoon and Paopairochanakorn, ⁴¹ 2006	Anaphylaxis incidence in ED	Yocum criteria ¹⁷⁰	ICD-9/10 codes and medical record review
Giannetti et al, ⁴⁸ 2021	Evaluation of patients referred for mast cell activation syndrome and hereditary alpha tryptasemia	NIAID plus unusual presentations ⁷⁹	Referred patients to 1 medical center
Francuzik et al, ⁵¹ 2021	Phenotype and risk factors for venom-induced anaphylaxis	NIAID	European Anaphylaxis Registry
Vos et al, ⁵⁶ 2017	Fatal anaphylaxis to yellow jacket in mastocytosis	Mueller Severity Classification, ¹⁷¹ 1966	Patients presenting with ISM presenting to 1 center
Volcheck et al, ⁵⁷ 2023	Perioperative anaphylaxis	Modified Ring and Messmer 4-step grading scale ^{21,172,173}	Review article
Mertes et al, ⁵⁹ 2003	Perioperative anaphylaxis	Clinical history (grade 3 or 4 as author defined) + skin test or slgE	Referred patients
Campbell et al, ⁷⁶ 2015	Risks of IV vs IM epinephrine for anaphylaxis	NIAID	ED patients 1 center
Macdougall et al, ⁷⁷ 2002	Incidence of severe and fatal food allergic reactions	Severity of allergic reaction used author-defined criteria	Death certificates; prospective survey
Grabenhenrich et al, ⁸⁶ 2018	Epinephrine use in severe allergic reactions	Ring and Messmer, ²¹ 1977	Anaphylaxis registry
Sampson et al, ⁸⁸ 1992	Fatal and near-fatal food allergy reactions	Author defined	Multiple reporting sources in 3 metropolitan areas
Epstein et al, ⁹¹ 2021	Risk factors for fatal and nonfatal reaction to SCIT	2008–2011: Author-defined grade 3 (3 total grades); 2012–2018: WAO immunotherapy grading system ²²	Survey of US allergists
Campbell et al, ¹⁰¹ 2015	Predictors of repeat epinephrine administration	NIAID	ED patients from 1 hospital
Nasr et al, ¹¹³ 2022	Management of anaphylaxis	WAO 2020 definition ⁹	ED patients from 1 hospital
Gabrielli et al, ¹¹² 2019	Prehospital management of anaphylaxis	NIAID	Anaphylaxis registry
Ditto et al, ¹²³ 1996	Idiopathic anaphylaxis	Author defined	Patients from individual center
Ditto et al, ¹²⁴ 1997	Idiopathic anaphylaxis	Author defined	Patients from individual center
Carter et al, ¹²⁶ 2021	Use of omalizumab in idiopathic anaphylaxis	NIAID	DBPC multicenter trial
White et al, ¹²⁸ 2018	Beta-blocker use and epinephrine doses required	NIAID	ED patients from 1 hospital
Smith et al, ¹³⁰ 2020	Anaphylaxis risk for cardiac catheterization for patients on BB or ACEI	Author defined	Single hospital cardiac catheterization lab
Sturm et al, ¹³¹ 2021	Effect of BB or ACEI on systemic sting or VIT adverse events	Ring and Messner, ²¹ 1977	Multicenter study
Ewan and Clark, ¹⁴⁰ 2001	Follow-up of peanut/tree nut allergy patients enrolled in management plan	Author defined (grades 1–5)	Referrals to tertiary allergy clinic
Ewan and Clark, ¹⁴¹ 2005	Follow-up of nut allergic patients enrolled in management plan	Author defined (grades 1–5)	Referrals to tertiary allergy clinic
Simons et al, ¹⁵³ 2009	Community survivors of anaphylaxis	Author defined as sudden onset severe allergic reaction as reported by patient	E-mail survey
Hourihane et al, ¹² 2021	Comparing cases of COVID-19 vaccination anaphylaxis based on definition of anaphylaxis	NIAID Brighton Collaboration, ¹¹ WAO 2020	COVID-19 vaccine task force published data
Lee et al, ⁷⁸ 2017	Anaphylaxis management disparities in 2 pediatric centers	NIAID	Anaphylaxis registry listing from 2 pediatric centers
Haerberli et al, ⁵³ 2003	bST in venom allergy relationship to anaphylaxis severity	Mueller Severity Classification, ¹⁷¹ 1966	Clinical study, unspecified
Guenova et al, ⁵⁴ 2010	bST as risk assessment in elderly patients with venom allergy	Mueller Severity Classification, ¹⁷¹ 1966	University allergy clinic
de Silva et al, ¹¹⁷ 2011	Use of AH, CS, epinephrine to prevent acute adverse reaction to snakebite anti-venom	Brown severity rating ²⁶	Patients at secondary hospitals in Sri Lanka

Abbreviations: AAFA, Asthma and Allergy Foundation of America Infant Anaphylaxis Study Criteria; ACEI, angiotensin-converting enzyme inhibitor; BB, beta-blocker; bST, baseline serum tryptase; COVID-19, coronavirus disease 2019; ED, emergency department; ISM, indolent systemic mastocytosis; NAP6, sixth National Audit Project of the Royal College of Anaesthetics; NIAID, National Institute of Allergy and Infectious Diseases; SCIT, subcutaneous allergen immunotherapy; slgE, specific immunoglobulin E; VIT, venom immunotherapy.

Table 4
Comparison of NIAID and WAO Criteria for Anaphylaxis

Item comparison number	Timing	Requires either "likely"/"highly probable" or "known" allergen	Symptoms/system	Meets NIAID	Meets WAO	Comment
1	Minutes to several hours	No	Skin and/or mucosal tissue AND respiratory compromise	Yes	Yes	SAME
2	Minutes to several hours	No	Skin and/or mucosal tissue AND reduced BP or associated symptoms of end-organ dysfunction	Yes	Yes	SAME
3	Minutes to several hours	No	Skin and/or mucosal tissue AND severe gastrointestinal symptoms (especially after exposure to non-food allergens)	No	Yes	DIFFERENT
4	Minutes to several hours	Yes, likely allergen	Skin and/or mucosal AND persistent gastrointestinal symptoms	Yes	No	DIFFERENT Similar to # 3 but subtle differences
5	Minutes to several hours	Yes, likely allergen	Respiratory compromise AND persistent gastrointestinal symptoms	Yes	No	DIFFERENT Partial overlap with #12, 13 for WAO, for example, if bronchospasm
6	Minutes to several hours	Yes, likely allergen	Respiratory compromise AND reduced BP	Yes	Yes	SAME
7	Minutes to several hours	Yes, likely allergen	Respiratory compromise AND symptoms associated with hypotension	Yes	No	DIFFERENT
8	Minutes to several hours	Yes, likely allergen	Persistent gastrointestinal symptoms AND reduced BP	Yes	Yes	SAME
9	Minutes to several hours	Yes, likely allergen	Persistent gastrointestinal symptoms AND symptoms associated with hypotension	Yes	NO	DIFFERENT
10	Minutes to several hours	Yes, known allergen	Reduced BP	Yes	Yes	SAME
11	Minutes to several hours	Yes, likely allergen	Reduced BP	No	Yes	DIFFERENT Similar to # 8 but different
12	Minutes to several hours	Yes, known, or likely allergen	Bronchospasm (excluded if inhalational reaction to aeroallergens or foods without ingestion)	No	Yes	DIFFERENT
13	Minutes to several hours	Yes, known, or likely allergen	Laryngeal involvement	No	Yes	DIFFERENT

Note: Bolded text indicates areas where the 2 guidelines differ in defining anaphylaxis.

Abbreviations: BP, blood pressure; NIAID, National Institute of Allergy and Infectious Diseases; WAO, World Allergy Organization.

patients with idiopathic anaphylaxis (IA), mastocytosis, or insect stinging anaphylaxis.^{46,47} HxT may be associated with an increased frequency and severity of anaphylaxis.⁶ In patients presenting with symptoms of IA, a baseline level of approximately 6.5 ng/mL has been suggested as the threshold to complete genotyping for HxT; however, this level still needs validation.⁴⁸ Furthermore, it has been proposed to use the TSAB1 copy number in conjunction with the bST to help determine whether a workup for clonal mastocytosis should be initiated in patients with IA.⁴⁹

In patients with IA or a known anaphylaxis trigger, such as, venom or drug allergy, who have a bST level more than 8, it has been suggested that a high-sensitivity peripheral blood D816VKIT mutation test should be obtained to screen for underlying mastocytosis.^{50,51} In that elevated bST levels are also noted in other disease states, such as, myeloid neoplasm, renal failure, and hypereosinophilic syndrome, this recommendation needs to be validated.⁵⁰

Owing to the unique association of venom hypersensitivity and, mast cell disorders, guidelines have recommended that physicians should consider obtaining a bST on all patients who are being considered for venom immunotherapy (VIT).^{52,53-55} More recently, it has been suggested that patients with mastocytosis without a history of stinging insect reactions should be tested for venom hypersensitivity and treated with VIT if they have a skin test positive result; however, thus far, there is no consensus or guideline recommendation to do so.⁵⁶

Anaphylaxis Data Collection

Anaphylaxis data collection is incomplete with important details, such as, reaction location (ie, restaurant); onset of symptoms after allergen exposure (ie, developed generalized urticaria and coughing 15 minutes after ingestion of an almond butter cookie with sesame seeds

on top); cofactors (ie, preceded by a 4 mile jog); comorbidities (ie, having asthma); initial and subsequent treatment by location (ie, 1 teaspoon of diphenhydramine administered at home 10 minutes after onset of symptoms, 2 puffs of albuterol administered by caretaker in private car on the way to the hospital, and 1 injection of 0.3 mg epinephrine administered by needle and syringe in an emergency department (ED) 35 minutes after onset of symptoms); and outcome (ie, symptoms worsened with wheezing noted on arrival in ED, improvement noted 10 minutes after epinephrine, full recovery 45 minutes after epinephrine, observed in hospital for 1 hour after full recovery, no biphasic reaction); often missing, preventing accurate epidemiologic analysis.^{3,38} Many times, data collection relies solely on International Classification of Diseases (ICD) codes, thereby omitting the detailed information relating to the anaphylactic episode.

Currently, we have no way to capture outpatient (without subsequent hospital care), nonfatal episodes of anaphylaxis, untreated or treated, with or without health care intervention. Designing such a reporting system will certainly be challenging.³⁸ It is important to capture "severe allergy reaction" and anaphylaxis, with a detailed description of the event. There is a need for standardized reporting terms/identifiers for location of anaphylaxis, such as, home, school, pre- and post-school, camp, restaurant, work, recreational setting indoors, recreational setting outdoors, and nonpatient home; the category of "other" should not be used. This reporting system needs to include all the recognized high-risk cofactors, such as, alcohol, menstruation, exercise, medications, mast cell disorders, and comorbidities such as cardiovascular disease and the use of BB angiotensin-converting enzyme inhibitors (ACEIs) for anaphylaxis.³ Complete and accurate data collection on anaphylaxis is needed to delineate risk factors further and to refine the clinical criteria and severity scoring of anaphylaxis.

Table 5
Representative Anaphylaxis Severity Rating Systems

Author/date published	Targeted allergen or treatment/population	# of grades	Development method	Advantages	Disadvantages
Mueller, ¹⁷¹ 1966	Venom/children	4	Expert opinion	Easy to understand and use in practice as grade 1 is “slight general reaction.” Grade 2 is a “general reaction”; grade 3 is “severe general reaction”; and grade 4 is “shock reaction.” Grades 2, 3, and 4 add 2 or more symptoms to the previous severity grade, creating a straightforward method of grading. System works best for venom reactions and better for food than drug challenge. System includes symptoms of impending disaster, presyncope (dizziness/weakness), and confusion.	This system has on-equivalency in the symptoms of each grade, for example, generalized urticaria and malaise (grade I) wheezing + dizziness vs nausea + vomiting (grade II) or dyspnea + feeling of impending disaster vs thickened speech + dysphagia (grade III). It is missing the symptoms of flushing, oral/palate itching and pruritus, nasal symptoms, stridor, and cough.
Ring and Messmer, ²¹ 1977 ----- Ring and Behrendt, ¹⁷⁴ 1999	Colloid volume substitutes (drugs)/all ages ----- All causes/all ages	4	Expert opinion Expert opinion	This system is easy to classify a patient if one uses the simplistic interpretation ¹⁷⁵ : grade: I—only skin; II—measurable but no life-threatening symptoms and various organs involved; III—shock or LOC; IV—cardiac or respiratory arrest.	The original grading system is difficult to use and is not valuable clinically as it is unclear when to administer epinephrine as grade I could include angioedema, site not specified, and grade II is very broad. This system focuses more on cardiovascular than respiratory symptoms. It is missing the symptoms of cough, stridor, oral/palatal/throat itching, presyncope (dizziness/weakness), confusion, and syncope.
Sampson, ²³ 2003	Oral food challenge/children	3	Expert opinion	This is an established grading system to which many other grading systems are compared. It allows researchers to include a broad range or symptoms within each organ system. It includes symptoms of oral/palatal itching.	Anaphylaxis is defined as any IgE-mediated symptom that develops after ingestion of a trigger which is very broad. This system fails to provide granularity for clinicians to assign a specific grade, based on the severity of the symptoms. It is missing the symptom of repetitive cough, crampy abdominal pain, confusion, and syncope.
Brown, ²⁶ 2004	All allergens/all ages	3	Logistic regression from retrospective cohort	This system is easy and quick to use in clinical practice as “mild” involves only skin and subcutaneous tissue; “severe” is identified by hypoxia, hypotension, or neurologic compromise, for example, confusion, incontinence, collapse, or LOC; and moderate is everything in between. This system may work better for food than drug challenges and correlates well with epinephrine use, for example, higher grade is associated with higher use of epinephrine. This system provides a clear clinical message to use epinephrine for all moderate and severe reactions.	This system lacks granularity for research studies in that moderate reactions cover multiple clinical symptoms and presentations. Subclassification of “mild” reactions is based on the presence or absence of angioedema, thereby increases the complexity of this simple system. The system recommends the use of epinephrine when angioedema is present.
Hourihane et al, ¹⁷⁶ 2005	Peanut oral challenges/children	3	Expert opinion	This system is very sensitive and specific, with a detailed scoring system for mild (1–5), moderate (6–13), and severe (14–25) anaphylaxis. The grade is based on the amount (mg) of peanut protein in skin/mucosal contact or ingested combined with symptom severity.	This system can only be applied to peanut allergic reactions and almost exclusively for oral challenge as the amount of peanut protein ingested in the community would be difficult to determine.
Ewan and Clark, ¹⁴¹ 2005	Tree nut or peanut/all ages	5	Expert opinion	This system makes it easy to classify reactions with grade 1 being mild, localized, cutaneous or oral pruritus; grade 2 is mild, generalized, cutaneous reactions; and grade 3 involves the addition of GI or rhinoconjunctivitis symptoms to a grade 1 or 2 reaction; grade 4, a moderate reaction, involves mild laryngeal edema or mild asthma; and grade 5, severe, involves dyspnea or hypotensive symptoms.	Grade 5 does not provide enough detail or levels of severity to adequately characterize anaphylaxis; therefore, this system has limited use for research or in clinical practice. Determining the effectiveness of a management plan after allergic reactions to tree nuts and peanut was the main objective of this observational study; the development of a severity grading system was a minor objective.
Muraro et al, ²⁴ 2007	All allergens/children	3	Position paper/expert opinion/consensus definition of anaphylaxis	This is a simple, widely used, 3-grade system that is comprehensive in listing of symptoms. It includes infant markers, for example, drooling and change in activity level. The grade is based on the organ system most severely affected and does not use a combination of symptoms. The system indicates where there should be mandatory use of epinephrine, for example, grade 2, laryngeal and moderate wheezing, and grade 3, hypotension, dysrhythmia, severe bradycardia, cyanosis, and cardiac or pulmonary arrest. This grading system works better for food than drug challenges as it emphasizes upper respiratory symptoms when evaluating severe reactions.	The authors provide limited background on the development process for this grading system. This system differs widely from earlier grading systems, as grade 1 is not limited to skin and mucosa but also includes nausea, drooling, nasal symptoms, throat itching, and sudden change in activity level. It is missing symptoms of repetitive cough and floppy baby. It requires measuring oxygen saturation and counting the pulse.

(continued)

Table 5 (Continued)

Author/date published	Targeted allergen or treatment/ population	# of grades	Development method	Advantages	Disadvantages
Cox et al, ²² 2010; Cox et al, ²⁸ 2017	SCIT/all ages	5	Task force/expert opinion	This system provides a detailed and extensive assessment of symptoms. When compared with other SCIT grading systems, it is considered the most comprehensive, factual, and reliable for both research and clinical data comparisons. Grade I symptoms can be from organ systems other than cutaneous. All grades are considered systemic reactions for which this grading system recommends epinephrine administration. The final report includes symptom at onset and the time of onset after SCIT and the time of epinephrine administration after onset of systemic reaction. It includes symptoms that are often omitted in grading systems, for example, metallic taste, uterine cramps, and not responding to inhaled bronchodilator.	The final grade is determined at the termination of event. The time to onset of reaction after SCIT does not factor into severity grade. This system does not require 2 systems of involvement to diagnose anaphylaxis, and therefore, using this system in clinical practice may be confusing for clinicians.
Cox for WAO2017 2017 ²⁸	All allergens/all ages	5	Task force/expert opinion	This revised version has similar advantages as WAO2010 (see previous texts) but excludes any recommendation on when to administer epinephrine. It is intended to be used for all triggers, not just SCIT. Grade I symptoms are well defined, and grade 2 is defined as symptoms from any 2 organ systems listed in grade 1.	WAO2017 has similar disadvantages as WAO2010 (see previous texts). This grading system was never endorsed by the WAO. This system correlates less with other severity grading systems than the WAO2010 version. Cough can fall into grade 1, 2, or 3 based on from where it derives. However, this may be confusing, as the physician and/or the patient may be unable to determine whether it derives from the upper or lower airway. The changes in grade numbering with the revised WAO2017 may be confusing: In WAO2017, grade 3 is very similar to WAO2010 grade 2, grade 4 is similar to WAO2010 grade 3, and grade 5 is similar to WAO2010 grade 4, and WAO2017 has no grade for death. The WAO2017 makes no recommendation on when epinephrine should be administered based on severity grading. It is missing symptoms of upper airway angioedema, hoarseness, presyncope (dizziness/weakness), confusion, and feeling of doom.
Niggemann and Beyer, ²⁹ 2016	All allergens/all ages	3	Expert opinion	This grading system is classified as 3 grades but with subcategories, it functions as 6 grades. This system is simple to use and suitable for daily practice as grade 1 is a local reaction (not anaphylaxis); grade IIA, a mild systemic (skin or GI); grade IIB, a moderate systemic reaction (skin and GI); and grade III, a severe systemic reaction (anaphylaxis). Grade IIIA involves mild respiratory or cardiovascular symptoms, grade IIIB involves moderate respiratory and/or cardiovascular symptoms, and grade IIIC is respiratory and/or cardiovascular arrest.	This system lacks granularity as not all symptoms are listed, for example, hoarseness, and neurologic symptoms, such as presyncope (dizziness/weakness), confusion, and feeling of impending doom. This system omits symptoms specific to infants. Ingested food without oral allergy syndrome and parental drug could never result in a grade 1 reaction in this grading system. It has confusing terminology, for example, redness is grade I but flush if grade II. Grade I uses a very subjective classification of symptoms, for example, angioedema is grade IIA, but cough is IIIA.

(continued)

Table 5 (Continued)

Author/date published	Targeted allergen or treatment/ population	# of grades	Development method	Advantages	Disadvantages
Hopkins et al, ¹⁷⁷ 2019	Anesthetic agents/ all ages	5 Clinical grades 5 Categories for serum tryptase	Delphi	This grading system is complex but is a well-defined total point scoring system for diagnosing perioperative anaphylaxis that determines a clinical grade and optionally adds serum tryptase values (peak compared with baseline) to arrive at a total score (0-32) It uses a formula of 1.2 x baseline + 2 ng to define an elevated tryptase level but also incorporates the upper limits of the normal reference range. The clinical point total is easy to calculate and understand, for example, >21 (“almost certain to be hypersensitivity reaction”) and <8 (“unlikely to be an immediate hypersensitivity reaction”). This system adds points for symptoms of 3 organ systems, the cardiovascular, respiratory, and dermal/mucosal. It subtracts points for confounders, for example, surgically induced hypotension, multiple attempts at tracheal intubation, and a patient on an ACEI having angioedema. It includes time interval between culprit exposure and onset of symptoms. It incorporates vital pieces of information for helping diagnose the culprit perioperative agent; however, the allergist would require the entire scoring sheet and not just the total point calculation, when evaluating a patient. This grading system includes definitions of terms used, for example, bronchospasm, severe bronchospasm, tachycardia, hypotension, and severe hypotension.	This grading system is only used for preoperative anaphylaxis with the total points/grade determined after the event. It is a very time-consuming scoring system to use as it incorporates 33 clinical assessments items and includes using both single and combined assessment items. The onset time for respiratory and cardiovascular symptoms must be recorded as used in the scoring system. Serum tryptase, acute and baseline, is strongly recommended to refine the total point grade. Implementation requires experience in interpreting anesthetic charts, preferably by someone not involved in the case to reduce bias. This grading instrument has not been validated. When relevant information is missing, the grading system will be less reliable. The statistical sensitivity of this grading system to detect an immediate hypersensitivity reaction because of either an immune (allergic and non-allergic) or a non-immune mechanism is unknown.
Blazowski et al, ¹⁷⁸ 2021	Food/children	4	Expert opinion	This system includes a comprehensive listing of 29 symptoms from 6 main organ systems (skin/mucosa, gastrointestinal, upper respiratory, lower respiratory, neurologic, and cardiovascular). To develop the new grading system, the severity of 315 community-based allergic food reactions was determined using 5 frequently used severity grading systems. The interrater reliability of classification between severity scores was assessed. Symptoms were grouped into a heat map analysis according to real-life incidence and clinical relevance. The symptoms listed and the grading are similar to Muraro et al, ²⁴ but this system also includes a few added symptoms, for example, pale and floppy child. Compared with Muraro et al, ²⁴ a new grade IV, for cardiac or pulmonary arrest, has been added. This new grading system indicates to administer epinephrine for rapidly progressing symptoms, even mild ones; for grade 1 when symptoms are from more than 1 organ system; and from all grade 2 to 4 reactions. The authors provide an easy-to-follow “traffic light” color-coded graphic to use for diagnosing anaphylaxis, determining severity, and treating with epinephrine, making it valuable for clinical practice.	This grading system is limited to food allergy and the authors caution against using it for other allergens. It has not been validated in different populations and the data have not been replicated. Oral food challenges were not done to confirm food triggers. Clinicians must recognize, as in Muraro et al, ²⁴ that grade 1 reactions are not limited to the skin and mucosa. Grade 2, 3, and 4 reactions do not consider skin and most mucosal symptoms but do consider laryngeal angioedema. All GI symptoms fall into grade 2, which is different from other grading systems; it has yet to be determined whether this is an advantage or disadvantage.

(continued)

Table 5 (Continued)

Author/date published	Targeted allergen or treatment/population	# of grades	Development method	Advantages	Disadvantages
Dribin et al, ³³ 2021	All allergens/all ages	5 with subgrading	Delphi	This grading system may be used for all allergens, in multiple clinical and research settings, and across all ages from infants to the elderly. This system creates a very specific grading scale broken down by number and type of organ system and symptom severity. The grades go from mild allergic to life-threatening reactions; however, the authors emphasize that this is independent of fulfilling diagnostic criteria for anaphylaxis. The symptoms within each severity grade represent near-equivalent reaction severity. This system uses the totality of symptoms to determine the overall reaction severity. It does not require a minimum number of organ systems to be involved to determine grade severity. This system is very granular, allowing for a detailed assessment as it uses subgrading based on well-defined clinical criteria. It is intended to be used at any time during the allergic reaction; however, the severity grade can change rapidly. This system includes detailed neurologic symptoms, for example, sense of impending doom, Glasgow Coma Scale, and includes specific symptoms for infants, for example, inconsolability, reduced activity, tongue thrusting, lethargy, and mottling. It does not use the treatment delivered and/or the treatment response, for example, to epinephrine or albuterol, in arriving at a severity grade. This system does not use symptom duration in determining severity grade. A pocket guide version is available.	This system uses 5 grades of severity and 24 subgrades to define the meaning of mild, moderate, and severe used within the 5 grades (excluding death). This creates a very complicated, time-intensive grading system. Even though multiple symptoms may be present within a specific grade category, the overall reaction severity is based on the most severe symptom which again adds to the complexity of this grading system. Using this grading scale during the reaction, as intended, may create multiple severity ratings as the reaction gets progressively more severe. The grading system offers no guidance on when to administer epinephrine. This system requires the use of another instrument, the Glasgow Coma Scale. This grading system requires objective examination of the tongue/palate/uvula and determination of percentage of skin involvement, for example, flushing, urticaria, and scratching, for defining localized vs generalized reactions. This system requires detailed counting of the episodes of diarrhea and vomiting. This system, in its current format, is unlikely to be used by clinicians in daily practice based on the complexity and time required both to assess and to document the components of the grade. This system will require decision support tools and an easy documentation template to facilitate incorporation into clinical practice. The use of medical terminology and assessments precludes the use of this grading system by the patient or caretakers. Patient perspectives were not included in the development of this grading system.
Chinthrajah et al, ³² 2022	Food allergy/oral food challenge and food immunotherapy/all ages	5	Expert opinion	This system is comprehensive but only grades systemic reactions (not local reactions). It uses more objective symptoms and more granularity than a previous instrument, CoFARV1. ¹⁷⁹ It minimizes investigator discretion in assigning grade, thereby reducing bias. The grades are broken down by number and type of organ systems involved and by severity of symptoms. It differentiates mild single system, for example, respiratory, reactions (grade 1) from mild multisystem reactions (grade 2) and factors in response to treatment, for example, albuterol or epinephrine. It incorporates a change in activity level and number of episodes of vomiting or diarrhea. The authors indicate that it may be used by investigators to help define anaphylaxis without using a separate definition or set of criteria. It is easier to use than the Dribin grading system.	This system has limited use outside of food allergy. It is detailed, time-consuming review of symptoms and treatment response, after termination of the adverse reaction to determine the final severity grade. It omits neurologic symptoms in the grading scale, for example, presyncope (dizziness/weakness), confusion, and feeling of doom and does not specify upper airway angioedema and hoarseness. In this grading system, unresponsiveness to treatment of lower respiratory symptoms is defined as requiring more than 3 doses of IM epinephrine or an IV infusion of epinephrine, a more aggressive definition than that used by other grading systems. It also seems quite subjective to define 2 episodes of vomiting as grade 2 and 3 episodes of vomiting as grade 3. Although this grading system is similar to WAO2017, there are some major differences, for example, mild abdominal pain is grade 1 in CoFARV3 but grade 3 in WAO2017.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; CoFAR, Consortium for Food Allergy Research version 3.0; GI, gastrointestinal; IM, intramuscular; IV, intravenous; SCIT, subcutaneous immunotherapy; WAO, World Allergy Organization.

Perioperative Anaphylaxis: Diagnosis and Treatment

Although most patients presenting with anaphylaxis have a wide differential diagnosis, POA has some unique diagnoses that must be considered including an overdose of anesthetic agent, major bleed, vagal stimulation, aspiration, fluid overload, and cardiovascular complications because of surgery, each presenting with similar and overlapping signs and symptoms.⁵⁷ Therefore, the first step when evaluating a patient who has experienced symptoms during surgery which are compatible with anaphylaxis is to establish that the diagnosis of POA is correct. Reviewing an acute ST level obtained in the operating room and a bST, drawn at least 24 hours later, can be very helpful in making the diagnosis of anaphylaxis; however, many times, this information is not available.

The allergist's evaluation of the etiologic agent(s) responsible for POA, using the history, combined with skin testing and challenge(s) to determine the responsible agent(s), is difficult. There are knowledge gaps as to which agents should be tested, including those used at the time of POA, and possible future alternative agents with potentially cross-reacting chemical structures; the most appropriate dose to use for testing; and the best timing for skin testing after POA. The lack of access to anesthetic agents for testing is a major hurdle for the community allergist. For many pharmacologic agents, such as, neuromuscular blocking agents, opioids, and antibiotics, it is unknown whether they induce mast cell degranulation through IgE or non-IgE-mediated mechanisms.^{58–61} It is also unknown whether the non-IgE-mediated reactions, such as, Mas-related G-protein receptor (MRGPRX2) activators, can be detected by skin testing. Although non-irritating concentrations for skin testing to many agents have been published, the positive and negative likelihood ratios have not been accurately determined, and the significance of a negative test result without a graded challenge is unknown.^{6,62,63} Unfortunately, the predictive value of graded challenges is also unknown. Waiting 4 to 6 weeks after POA before skin testing is based solely on case series and reports involving insect and drug allergy.^{64,65}

Skin testing is recommended over *in vitro* testing when evaluating agents responsible for POA, but there is a need for validated, highly sensitive, and specific *in vitro* tests for perioperative pharmacologic agents.⁶⁶ Although both the ImmunoCAP FEIA sIgE assay and the BAT to individual neuromuscular blocking agents have excellent specificity, they have much lower sensitivity.⁶⁶

The allergist also needs a decision tool when skin testing and/or challenges cannot be completed, but the patient requires repeat surgery, and the allergist must recommend the safest agents to be used. POA provides a unique opportunity for future research to determine the benefit of advanced treatment modalities for refractory anaphylaxis, such as, vasopressin and methylene blue, in a controlled setting.⁴⁸ Furthermore, the value of premedication with antihistamines, corticosteroids, and antileukotriene agents to prevent the development of or severity of anaphylaxis remains uncertain for all types of anaphylaxes, including repeat surgery after POA, and requires further study.

Biphasic, Refractory, and Persistent Anaphylaxis and Emergency Department Observation Time

The definitions of biphasic, refractory, and persistent anaphylaxis are highly variable, based predominantly on expert opinion. Reaching consensus on how to define these types of anaphylaxes is the first step in understanding the relationship, or lack thereof, that the treatment of acute anaphylaxis has to their development and in determining how to prevent or at least predict the development of biphasic, refractory, and/or persistent anaphylaxis. The lack of an objective, universally accepted definition of biphasic reactions likely accounts for the variability in reported rates (1%–19%) and identified risk factors.⁶⁷ There needs to be expert consensus on the lower- and upper-

time thresholds for defining biphasic anaphylaxis after recovery from initial anaphylaxis. When symptoms resolve without the administration of epinephrine but then return, for example, 2 hours after, there is disagreement as to whether this constitutes a biphasic reaction.

Using a Delphi process, one panel of anaphylaxis experts reached consensus that epinephrine was not required to have been used during the initial treatment of anaphylaxis before one could establish anaphylaxis and that the lower and higher time thresholds should be 1 hour and 48 hours, respectively.⁶⁷ Although epinephrine is not always administered during anaphylaxis, for example, it is unavailable, all anaphylaxis treatment guidelines recommend that epinephrine be used as first-line treatment when anaphylaxis is present.^{9,68–71} In fact, if there is doubt about a serious allergic reaction being anaphylaxis, epinephrine should, nonetheless, be administered.

The definition of refractory anaphylaxis also varies as it is usually based on some combination of the number of epinephrine doses required, for example, 2 or 3; the mode of epinephrine administration, for example, intramuscular or intravenous; additional treatment provided, for example, intravenous fluids and oxygen; and/or the passage of time since onset.⁶⁷ There is no consensus on the duration of ongoing symptoms of anaphylaxis and the extent of previous treatment that is required before a patient is diagnosed to have persistent anaphylaxis.⁶⁷

There are no prospective trials or validated prediction models for determining the ideal observation time in the ED or when hospitalization is indicated. The rationale for ED observation of a patient who has had complete or nearly complete resolution of initial anaphylaxis is usually to observe for a biphasic reaction. Biphasic anaphylaxis is more likely to occur with increasing anaphylaxis severity and in patients who have received more than 1 dose of epinephrine for anaphylaxis treatment.⁷² Additional risk factors, for example, wide pulse pressure, unknown trigger, delayed treatment with epinephrine, hypotension as the presenting symptom, and drug allergy in children, have been found in some but not all studies.^{72,73} Validation of risk factors for biphasic anaphylaxis and an agreed on severity scoring system is needed. There is also a need for a consensus-derived algorithm for determining an individual patient's ED observation time based on a risk/benefit assessment.

Gaps in Treatment of Anaphylaxis

Epinephrine: Use, Route of Administration, Dosage, Needle Length, and Timing

Epinephrine is considered the first-line treatment for anaphylaxis, but a 2020 systematic review identified only observational studies on the efficacy of epinephrine for anaphylaxis, and these had a high risk of bias.⁷⁴ However, owing to ethical considerations, we will not find RCTs on either efficacy, route of administration, dosage, or needle length. Intramuscular epinephrine administration is recommended over subcutaneous administration based on higher plasma levels; however, the evidence was of low certainty, as it was not studied in patients during anaphylaxis, used different injection sites, and used different depths of injection.^{74,75} In the ED, guidelines indicate that the intramuscular route is preferred over the intravenous route unless there is complete cardiovascular collapse, as intravenous epinephrine is associated with a 13% higher risk of overdose, an 8% increase in cardiovascular events, and with fatalities when inappropriately used.^{9,68–71,76–78}

Epinephrine 0.01 mg/kg, with a maximum of 0.5 mg in adults and 0.3 mg in children, administered intramuscularly into the anterolateral thigh is the first-line drug to treat anaphylaxis; however, this dose was derived empirically and is based on expert consensus.^{14,79} Although most guidelines worldwide agree with this dose when administered by a needle and syringe, for example, in a hospital setting, the prescribed EAI dose is often much lower, due, in part, to the

limited variability of fixed-dose EAI available in each country. In the United States, with only the adult 0.3 mg EAI being available, a 150 kg adult would receive only 0.002 mg/kg, whereas in the United Kingdom, with the available 0.5 mg EAI, this same adult would receive 0.003 mg/kg, still lower than the 0.01 mg/kg dose.⁸⁰ The dosing guidelines for infants and young children also vary by country, as an 8 kg infant would be prescribed a 0.1 mg dose in the United States, compared with a 0.15 mg dose in Europe, Canada, and Australia, whereas a 27 kg child would receive 0.15 mg in the United States compared with 0.30 mg in Europe, Canada, and Australia.⁸⁰ However, there have been no data indicating that the 0.15 mg dose delivered to infants weighing less than 7.5 kg is unsafe, even though this would exceed the 0.01 mg/kg standard.⁶ The longer needle length in the 0.15 EAI compared with the 0.10 EAI has been considered potentially to increase the risk in young infants for a needle embedment in bone or an intraosseous injection, although this has not been documented.^{81,82,83} In overweight or obese adults, especially in women who have increased subcutaneous fat compared with men, the skin-to-muscle distance often exceeds the EAI needle length, thereby increasing the risk for a subcutaneous injection which is associated with a slower systemic distribution compared with intramuscular administration.⁸⁰ The reported increased community anaphylaxis fatalities in obese women may be partially related to both an inadequate dose and needle length.^{4,80,84} The Resuscitation Council of UK has made a strong recommendation, but with a low certainty of evidence, for 0.50 mg intramuscular to be the preferred epinephrine dose for adults.^{4,85} In one crossover study in healthy adults, EpiPen 0.3 mg, a cartridge-based device, resulted in a significantly higher Cmax and quicker time-to-peak concentration than did Emerade 0.50 mg, a high-tension syringe-based device.⁸⁵ There have been no head-to-head comparisons of Emerade 0.50 mg and EpiPen 0.30 mg for the treatment of anaphylaxis; therefore, no recommendation can be made in favor of one over the other.

Meeting a specific definition or set of criteria for anaphylaxis diagnosis should not be a requisite for the use of epinephrine during a serious allergic reaction, and delaying administration may result in progression of symptoms.^{86,87} Early treatment with epinephrine may be more effective in treating the initial anaphylaxis, and in preventing the development of a biphasic reaction, and it has been associated with better outcomes.^{72,88–90} Based on fatal and nonfatal anaphylactic reactions to food and anaphylaxis-induced cardiovascular shock in canines, delayed epinephrine administration, for example, at maximum hypotension, may have limited to no effect on cardiovascular collapse.^{27,89}

There is a need for a consensus-based, point-of-care, and patient-observed list of signs and symptoms that indicates exactly when to administer epinephrine during a severe allergic reaction or evolving anaphylaxis. As part of the patient-specific (vs generic) AEP, this list may need to be based on previous reactions, treatment responses, comorbidities, and cofactors. A consensus-based generic AEP will need to consider the risk/benefit for the entire allergic population and will likely include a lower threshold for epinephrine administration.

Prescription of Epinephrine Autoinjectors: When and How Many

Risk stratification decision aids are needed to assist clinicians in determining criteria for prescribing epinephrine for specific indications, for example, oral allergy syndrome; all or select patients on allergy immunotherapy (AIT), and food-induced localized urticaria, and for which symptoms observed during persistent and/or biphasic anaphylaxis.⁷

It is estimated that all patients on subcutaneous immunotherapy (SCIT) have a risk of 0.8%⁹¹ to 7%⁹² for a systemic reaction, a 1.5% risk for a severe reaction,⁹² and a 0.01% risk for a near-fatal reaction.⁹¹ Delayed reactions from SCIT in some patients have been reported by

80% of US allergists.⁹³ Small US surveys have revealed that for inhalant SCIT, allergists prescribe EAI as follows: 29% to 33% for all patients, 53% risk stratified, and 14% never prescribe.^{93,94} A recent US survey of otolaryngologic allergists revealed that 80% prescribe EAI for all SCIT patients, 12% only to high-risk patients, and 2% to no SCIT patients.⁹⁵ Currently, the Joint Task Force on Practice Parameters (JTFPP), the American Academy of Otolaryngologic Allergy (AAOA), and the European Academy of Allergy and Clinical Immunology (EAACI) recommend risk stratification but without specific guidance as to how to complete this risk assessment.^{96–98}

Currently, in both the United States and United Kingdom, prescribers only have the option of prescribing 2 EAI for all patients; however, single-dose units are available in other countries, for example, Canada. The European Medical Agency also commends the prescription of 2 EAI for anaphylaxis. In a meta-analysis of 50 studies, multiple doses, most frequently 2 doses, of epinephrine were required in 7.7% of cases with 3 or more doses administered 2.2% of the time; the studies had a low risk of bias but moderate-to-high heterogeneity.⁹⁹ In the community setting, for food- and venom-induced anaphylaxis that required at least 1 dose of epinephrine, further doses were required in 12.3% and 17.9% of patients, respectively.⁹⁹ Unfortunately, there are limited data on where and who administers the second dose of epinephrine. One patient survey found that 58% of second doses were administered by the patient.¹⁰⁰ Potential reasons for requiring more than 1 dose include operator error with administration; a history of previous anaphylaxis with flushing, diaphoresis, and/or dyspnea; reaction progression; underdosing with the prescribed EAI; subcutaneous injection; delayed administration; and biphasic reaction.^{4,99,101} Using a Markov model for cost-effectiveness, prescribing 2 EAI for all patients with peanut allergy, at the current US price, was not cost-effective when compared with stratifying risk based on previous anaphylaxis history and/or having previously required multiple doses of epinephrine.¹⁰²

Epinephrine Underuse and Accidental Injury From Epinephrine Autoinjectors

In a systematic review and meta-analysis of 86 studies, 74% of which reported reactions in the community setting, it was found that anaphylaxis was treated with epinephrine in 50.4% of cases.⁹⁹ However, based on a 10-year analysis of 10,184 anaphylaxis incidents, only 27.1% of health professionals and 14.7% of patients/caretakers administered epinephrine for anaphylaxis.⁸⁶

Professionals administered epinephrine more often when the onset of symptoms was less than 10 minutes.⁸⁶ Reasons patients and lay caretakers provided for not receiving epinephrine were EAI available, but not used (22.4%); EAI prescribed but not available (4.7%); and EAI not prescribed (72.8%).⁸⁶ Other studies have revealed that when prescribed, the parental carrying rate for children was 44% to 58% (always carry at least 1)^{103–105} but that this rate can be improved with an intense quality improvement initiative.¹⁰⁴ Patients with repeated reactions to the same allergen and trigger confirmation by diagnostic testing were more likely to receive epinephrine, whether self-administered or given by a health care professional.⁸⁶ Caretakers were less likely to use EAI in preschoolers than in the elderly.⁸⁶ The patient's psychological stress was the only cofactor that resulted in increased use of epinephrine by professionals.⁸⁶ Severity rating was strongly associated with the use of epinephrine by professionals, with 66.9% of near-fatal (grade IV) reactions receiving epinephrine.⁸⁶ Future studies should collect data on which factors or circumstances led professionals and patients to administer or not administer epinephrine.⁸⁶ Once these data are collected, validated strategies to increase the use of epinephrine during anaphylaxis need to be developed.

With EAI use, lacerations, bent and bone-embedded needles, and thumb injections occur because of unintended patient movement,

operator error, or device malfunction, and more research is needed for ways to avoid these risks.^{81,106,107,108} The ideal frequency and method for training patients and caretakers in the use of EAI are unknown.

Anaphylaxis Treatment: Beyond Epinephrine

Antihistamines (AH) and corticosteroids (CS) are more frequently used than epinephrine in both the community and in the ED for the treatment of acute anaphylaxis, but there is little evidence supporting their use.^{9,109–112,37,113} AH and CS do not resolve respiratory or cardiovascular symptoms or improve survival, often delay the administration of epinephrine, and may increase morbidity.^{112,114,4,72,115,116} In the absence of any RCTs revealing benefit, guidelines and systematic reviews have placed both AH and CS as second- or third-line agents or have recommended against their use.

There has been 1 randomized trial that studied the effect of pretreatment with antihistamine and/or corticosteroids on severe allergic reactions, including anaphylaxis. A double-blind, placebo-controlled randomized trial of 1007 post-snakebite hospitalized patients in Sri Lanka used antihistamines (promethazine 25 mg intravenously) and corticosteroids (hydrocortisone 200 mg intravenously), both alone and in combination, immediately before the administration of snake anti-venom, and there was no reduction in the rate of adverse reactions to anti-venom compared with placebo.¹¹⁷ However, pretreatment with epinephrine 0.25 mg subcutaneously reduced severe reactions by 43% at 1 hour and by 38% more than 48 hours.¹¹⁷ When hydrocortisone was combined with epinephrine as a pretreatment, there was no reduction in adverse reactions.¹¹⁷

Systematic reviews do not reveal any benefit for AH and CS in preventing biphasic reactions or reactions to low or non-isomolar radiocontrast agents.^{99,118,72,114} However, premedication using AH and/or CS continues to be used for rush, and, at times, for conventional AIT, radiocontrast media, chemotherapy, and repeat surgery after POA.^{119,96,72,120} A combination of H₁ and H₂ AH, CS, and leukotriene blockers is the initial treatment for persistent systemic mastocytosis.¹²¹

It has been suggested that RCT or at least prospective observational trials should be designed, for example, for treatment of acute anaphylaxis in the ED or for oral food challenges in academic centers, to provide conclusive evidence for what role AH and CS play in prevention or treatment of acute anaphylaxis, whether as single agents or when combined with epinephrine.

Other supportive therapies, intravenous fluids, and supplemental oxygen are often used in the treatment of anaphylaxis, preferably before the development of hypotension. When available, many clinicians would start oxygen and intravenous fluids after the second administration of epinephrine. However, we lack evidence regarding exactly when in anaphylaxis treatment intravenous fluids and oxygen should be started. There is also a need to determine how the timing of epinephrine and supplemental treatments affects the compensatory mechanisms responsible for anaphylaxis.

Idiopathic Anaphylaxis: Treatment and Prevention

Idiopathic anaphylaxis, a diagnosis of exclusion, represents approximately 20% of all cases of anaphylaxis.¹²² Epinephrine remains the first-line treatment for acute episodes, with a combination of H₁ and H₂ AH as second-line treatment.¹²² To help prevent frequent and severe episodes and for chronic symptomatic idiopathic anaphylaxis, the recommended step-wise treatment, based on case reports and small prospective studies, is daily high-dose H₁ AH, and, at times, H₂ AH, anti-leukotriene agents, and/or corticosteroids.^{122,123,124} In select cases, ketotifen, oral cromolyn, and oral albuterol have been used.¹²⁵ However, no combination has reliably prevented recurrent acute

episodes.¹²⁶ Biologics, including omalizumab, dupilumab, and rituximab, are being studied, but results to date are inconclusive.^{126,122} Until there are enough trials to provide an evidence-based treatment approach, clinicians could benefit from a consensus-based treatment algorithm for IA.

Beta-Blockers and Angiotensin-Converting Enzyme Inhibitors/Receptor Antagonists: Role in the Incidence, Severity, and Treatment of Anaphylaxis

BB and ACEI have physiological effects that could theoretically increase the risk and severity of anaphylaxis; therefore, physicians have been concerned about using them in patients at risk for potential anaphylaxis, for example, venom and inhalant immunotherapy, drug challenges, and IA. However, the data are inconclusive, based partially on the failure of many studies to adjust for underlying cardiovascular disease, a known risk factor for severe anaphylaxis.^{127,92,128,129,130} A recent systematic review and meta-analysis of 21 observational studies of anaphylaxis (all causes) found that BB and ACEI were significantly associated with increased severity but not with increased incidence of anaphylaxis; however, this study was not adjusted for cardiovascular risk.⁹² Similarly, a large case-controlled study revealed a higher frequency of severe cardiovascular anaphylaxis with BB or ACEI use, but this was correlated with preexisting cardiovascular disease.⁵¹ In contrast, a large prospective observational study of patients with insect sting anaphylaxis found that patients on BB or ACEI had no increased severity of anaphylaxis to live stings before or during VIT; furthermore, they had no increased frequency of systemic adverse events to VIT.¹³¹

When comparing drugs, beta-1 selective BB may pose less risk than nonselective BB, angiotensin receptor blockers may pose less risk than ACEI, ACEI may be less risky than BB, and using both ACEI and BB concurrently may have the greatest risk, but there are inadequate studies to provide a definitive answer.^{132,130,133} When considering treatment, it is unlikely that BB interferes with the effectiveness of epinephrine as treatment of anaphylaxis, as there is no evidence that these patients have required additional doses of epinephrine.¹²⁸

For VIT, cardiovascular disease seems to be the main risk factor for anaphylaxis and not the medications used to treat this disease, providing a rationale to initiate and to continue VIT, potentially indefinitely, in these patients without modification of their BB and ACEI medications. The use of BB/ACEI during sublingual immunotherapy is not associated with increased severity or frequency of systemic reactions; their use in SCIT does not increase the frequency but may increase the severity of the reaction.¹²⁷ Patients on SCIT and BB/ACEI may have a 40% higher relative risk for a severe reaction; however, patients on SCIT with cardiovascular disease have a 3- to 5-fold higher risk than do those taking BB/ACEI.^{6,92} Therefore, the absolute risk is likely to be very low and the morbidity from inadequately treated cardiovascular disease may pose an even greater risk.

There is insufficient evidence with which to determine the risk of BB/ACEI during drug desensitization, and the evidence of their role(s) during radiocontrast media administration is inconclusive. A recent case-control study found that patients on BB or ACEI undergoing cardiac catheterization with low osmolar RCM did not have increased frequency or severity of anaphylaxis.¹³⁰ The risk of BB/ACEI in patients with IA and mast cell disorders is unknown. Although these drugs may increase the severity in food-induced anaphylaxis, there may be an increase in overall mortality because of cardiovascular disease, if they are discontinued.^{134,135}

For anaphylaxis management in general, the indications for the BB/ACEI and the indications for the diagnostic and/or therapeutic intervention must be balanced with the potential benefit of each and the risk of no treatment or intervention. However, no evidence-based

algorithm exists to assist the clinician in this shared decision-making conversation with the patient. In most cases, the risk of stopping the medication is greater than the risk of more frequent or severe anaphylaxis if continued, but this does vary from patient to patient, depending, for example, on the frequency of exposure.

Anaphylaxis at Home and in the Community

Recognizing that 72% of anaphylaxis fatalities occur in places other than the home and hospital, it has been suggested that undesignated EAls be available in multiple public areas, for example, schools, restaurants, recreational facilities, airplanes, and shopping malls.³ Although many states permit undesignated EAls in community settings, their presence is rarely mandated, and medicolegal issues, particularly for prescribing physicians, have been inadequately addressed. Furthermore, the most efficient implementation methods, cost-effectiveness, and funding sources for providing EAls in public areas are unknown. There are limited evidence and no consensus on the content, format, delivery method, and frequency of training programs on anaphylaxis for implementation in community settings.^{136–138} The effectiveness of existing training programs in improving anaphylaxis outcomes has not been studied.

It has been recommended that childcare centers and schools stock undesignated EAls and provide personnel training in allergy and anaphylaxis management, including the use of EAls.¹³⁹ Although studies are limited and have a low certainty of evidence, such training may reduce the rate of allergic reactions and the need for epinephrine in students.^{139–141,142,143,144,145,146}

The validity of the information about and the value of medical allergy jewelry or cards are often questioned. It is unknown whether they reduce the risk or improve outcomes of anaphylaxis.^{147,148}

Once approved, alternative delivery methods of epinephrine, such as, sublingual and intranasal, should be studied for their acceptance and timely use in community settings and for their impact on improving anaphylaxis outcomes. One intranasal epinephrine product has obtained Federal Drug Administration new drug application status, and other intranasal and sublingual products are under development.^{7,149–152}

Anaphylaxis Emergency Plans and Anaphylaxis Education

Although international, for example, WAO, regional, for example, EAACI, and national, for example, United States and Australia, guidelines all recommend a written AEP or action plan, they rarely endorse a specific AEP and fail to specify the specific components that should be included. Although such a plan is strongly recommended, only 39% of patients with diagnosed anaphylaxis possess a written emergency plan.¹⁵³

Multiple knowledge gaps exist in the prevention and treatment of anaphylaxis, including the evidence-based benefit of AEPs; the need for multiple types of AEPs, such as, generic and/or personalized; the most ideal format for the form; key components that are required and those that are optional; specific symptoms for which epinephrine and/or antihistamines should be administered; reflex vs non-reflex seeking of emergency care after use of EAI; and format and frequency of patient/community educational sessions on anaphylaxis.

A 2008 systematic review of 19 self-management AEPs found a wide range of perspectives, a potential for harm and weak evidence for their clinical benefit, and cost-effectiveness.¹⁵⁴ The authors suggested that a RCT should be completed to establish clinical value before proffering universal recommendations for their use.¹⁵⁴ In schools, AEPs may help reduce the rate of allergic reactions and the need for epinephrine use in students.^{139–141,142,143,144,145,146} Prevention strategies are often included on individual, personalized AEPs for students. Recent guidelines on prevention and management of allergic food reactions in schools conditionally recommend against classroom-level food bans and allergy-free tables, except for students who cannot self-manage because of their very young age, cognitive limitations, or physical impairments.¹³⁹

In 2010, a multidisciplinary, 25-member expert panel used e-Delphi to create a list of the 12 key components to be included in an AEP, including how to recognize and to treat anaphylaxis based on the severity of the reaction¹⁵⁵ (Table 6). They recommended both a short, simple, generic plan for crisis situations and a patient-specific, negotiated, more detailed, long-term AEP.¹⁵⁵ A 2017 systematic review identified 41 AEPs in English, 10 of which were from the United States or Canada.¹⁵⁶ They were developed by a variety of nongovernmental agencies, for example, national allergy societies, patient advocacy groups, educational bodies, and pharmaceutical companies.¹⁵⁶ These plans were analyzed for the e-Delphi 12 key components, with most falling short; for example, US AEPs had only 2 to 8 of the recommended 12 key components.¹⁵⁶ Most of the AEPs were personalized plans (78%), with the remainder being generic.¹⁵⁶ Most AEPs gave different instructions for mild vs severe reactions and 37 individual symptoms of anaphylaxis were listed across the different AEPs.¹⁵⁶ Currently, a number of AEPs are available from organizational websites, such as those of the American Academy of Pediatrics, Food Allergy Research & Education, American Academy of Allergy, Asthma & Immunology, and American College of Allergy, Asthma and Immunology/Allergy & Asthma Network, and each has varying formats, components, and listed symptoms.

Patients underuse EAls for a variety of reasons, including lack of comfort in recognizing anaphylaxis and implementing the EAI, fearing epinephrine adverse effects, and not wanting to activate emergency medical services (EMS)³⁹ after the use of the EAI.^{157,158} There is a general agreement that patients benefit from clinician-provided education and counseling on identifying and self-treating

Table 6
Consensus on the Components to be Included in an Anaphylaxis Emergency Plan (in Rank Order)

Component number	Components to be included in a patient-specific anaphylaxis emergency plan	% consensus
1	Contact details of family members (names, phone #s)	100%
2	Details about patient's allergy triggers	100%
3	If drug allergy, list of generic and proprietary names and cross-sensitizing drugs	100%
4	Signs and symptoms of mild, moderate, and severe allergic reactions and actions to take for each category of severity	100%
5	Prescribed medications and when they are to be used	100%
6	Management of emergencies: actions to be taken and medications to be used	100%
7	Clear statement to administer epinephrine without hesitation	100%
8	When to call emergency medical services	100%
9	Where medication is stored, eg, home, school, workplace	96%
10	Date that medications were last reviewed	87%
11	Number of epinephrine autoinjectors required	83%
12	Who is trained to administer medication in home, school, and workplace	80%

NOTE. Modified from Worth Table 2.¹⁵⁵

anaphylaxis; however, the format and frequency of these educational sessions have yet to be determined.^{159–162}

There is a need for a consensus-based, point-of-care, patient-observed list of signs and symptoms that indicates exactly when to administer epinephrine during a severe allergic reaction or evolving anaphylaxis. As part of the patient-specific (vs generic) AEP, this may need to be based on specific triggers, previous reactions and treatment response, geographic location and local setting, comorbidities, and cofactors.

A generic AEP to be used in restaurants, camps, airplanes, and, possibly, schools, will need to consider the risk/benefit for the entire allergic population and will likely need to set a lower threshold for epinephrine administration. There is a need for a global, consensus-derived, generic AEP that provides a simple, clearly stated indication for when and how to use the EAI and actions to take thereafter. It is unknown whether including AH or patient-specific considerations on the AEP, for example, for school settings, improves outcome.

As one critical component of an AEP, the patient should be instructed to use epinephrine. The use of intramuscular epinephrine is generally safe, even for patients with advanced age and/or cardiovascular risk factors, and there are no absolute contraindications for its use during anaphylaxis because adverse events are typically mild and transient with serious adverse events likely to occur at a rate of only 0.73%.^{76,163,164,92,131,165} Combined with the evidence that the severity of previous anaphylaxis and the initial presenting symptoms do not predict the ultimate severity of a specific anaphylactic event, early administration of epinephrine during an allergic reaction, even before there is a confirmed anaphylaxis, should be considered.⁷²

Most AEPs include summoning EMS after the use of the EAI; however, there is a lack of evidence for the benefit of universal EMS activation, it is unlikely to be cost-effective, and it may dissuade patients from using EAI.^{39,166} It has been suggested that activation of EMS after the use of an EAI in lower risk patients may not be necessary when there is prompt, complete, and durable response to treatment; there is access to advanced medical care; and additional EAI are readily available.^{6,166–168}

Conclusion

Although many knowledge gaps remain in the diagnosis and treatment of anaphylaxis, top priority should be given to global, consensus-derived definition/criteria for diagnosing anaphylaxis and for a generic and patient-specific (modifiable) AEP.

In addition to diagnosing and treating anaphylaxis, it is important to determine which patient-oriented outcomes are most important before one can evaluate current and new therapies for prevention and treatment of anaphylaxis. The physician-provided education and the patient-specific AEP must be consistent with the individual's racial, cultural, and socioeconomic background. The physician needs to have an established mechanism for assessing and addressing the psychological impact of the anaphylaxis diagnosis and treatment on the patient and their caretakers. For each patient to achieve the highest quality of life, it is necessary to assess and to balance each patient's perception of risk and the burden and barriers to effective prevention and/or treatment of anaphylaxis.

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