Anaphylaxis: Definition and criteria

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ABSTRACT

Anaphylaxis is a systemic allergic reaction that may be severe and life-threatening. With more than a dozen anaphylaxis definitions proposed over the past several decades and several diagnostic criteria in circulation, there is a need for a multinational consensus definition to simplify management across specialties. Anaphylaxis diagnostic criteria are more alike than they are different, and approaches of the National Institute of Allergy and Infectious Disease, World Allergy Organization, and Brighton Collaborative help to add granularity and perspective to patient management. Anaphylaxis occurs across a spectrum of severity within populations, although, among individual patients, there is some evidence to suggest more consistency for an individual allergen. Still, severity is influenced by a number of factors that demonstrate variability: factors that relate to allergen triggers, patient characteristics, and treatments received. Severity of anaphylaxis impacts management, and recent guidelines provide approaches that consider individual factors to inform both strong and conditional recommendations. Conditional recommendations serve as navigational signals for shared decision-making when patient expertise is leveraged to inform individual preferences and values together with clinician expertise in anaphylaxis management to provide patient care bespoke to each patient. As novel approaches to both prevention and treatment of anaphylaxis emerge, an understanding of the significance of strong and conditional recommendations becomes critical to providing individualized and appropriate care for patients at risk for anaphylaxis.

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Anaphylaxis is a systemic allergic reaction that is often sudden and frightening for patients and families.[1,2] With up to 1 in 20 individuals experiencing anaphylaxis, the impact of the disease and societal health burden is significant.[2–6] Triggers for severe allergic reactions are diverse across populations, with common triggers, which including medications, foods, and insect stings.[2–7]

Recent decades have witnessed progress in our understanding of anaphylaxis prevention and management, and we stand on the precipice of even greater advances that leverage both patient-preference sensitive care in conditions of clinical equipoise as well as new technologies for both prevention and treatment of severe allergic reactions.[8–14] Still, fundamental questions remain in anaphylaxis diagnosis and classification, and these uncertainties have a direct impact on patient counseling and treatment of anaphylaxis.[1] This review provides an update on current anaphylaxis diagnosis with an emphasis on translatable and actionable advice that can be used to improve care of patients at risk.

ANAPHYLAXIS DIAGNOSTIC CRITERIA

There continues to be great interest in formulating a set of universal multinational anaphylaxis criteria.[1] This is a laudable and important goal because a single set of anaphylaxis criteria will simplify management across medical specialties and facilitate timely and appropriate care.[1] When considering a simple description for anaphylaxis alone, no less than 15 definitions have been proposed over the past 2 decades.[1] At present, there are at least three distinct criteria for anaphylaxis in use. These include the National Institute of Allergy and Infectious Disease (NIAID), World Allergy Association (WAO), and Brighton Collaborative Criteria (BCC).[1,15–17] Although each of these definitions and criteria add granularity to our understanding of systemic allergic reactions, having a unified approach to evaluation and management of patients across the globe would represent progress.[1]

The best known and most-used set of anaphylaxis criteria in the United States are the 2006 NIAID criteria that set forth three circumstances in which anaphylaxis is highly likely: (i) sudden mucocutaneous (*e.g.*, urticaria) signs with respiratory or cardiovascular compromise, (ii) two or more organ systems involvement in an acute reaction after exposure to a likely allergen, or

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(iii) reduced blood pressure after exposure to a known allergen.[1,16] The 2020 WAO criteria are similar to that of the NIAID but with only one of two conditions that need to be met.[1,15] Similar to NIAID, anaphylaxis is considered highly like when either criteria is met: (i) acute onset of mucocutaneous signs (*e.g.,* urticaria) with either airway/breathing, circulation (*e.g.,* cardiovascular compromise), or severe gastrointestinal involvement; or (ii) sudden laryngospasm or bronchospasm after exposure to a highly probable allergen (Table 1).[1,15] Notably, neither of the first criteria of either NIAID or WAO require a suspected allergen exposure but subsequent criteria of each diagnostic set do include this stipulation.[1,15,16] The NIAID diagnostic criteria[18] were reported to have a 95% sensitivity (Sn) with a 71% specificity (Sp) in a prospective validation study of emergency department patients.

The 2007 BCC, developed for the diagnosis of anaphylaxis after immunization, were frequently used early in the COVID-19 pandemic; however, due to poor in overdiagnosis of anaphylaxis during the pandemic, the criteria were recently revised.[1,17,19] The criteria were and continue to be a bit cumbersome to use clinically and usually require access to a grading table for the level of certainty assignment (level 1 to level 5) by using a variable combination of major and/or minor criteria. In a study that compared the 2007 BCC with the 2006 NIAID criteria a discordant diagnosis of anaphylaxis was found in 28.1% of cases.[1,20] To address limitations in Sp, in 2022, the BCC[17] was updated to be more consistent with common case definitions of anaphylaxis.

Confirmatory testing is helpful in evaluation of severe allergic reactions; however, such testing is not necessarily a surrogate marker for anaphylaxis, which remains a clinical diagnosis.[1,7] The Allergy Immunology Joint Task Force on Practice Parameters (JTFPP) 2023 Anaphylaxis Practice Parameter Update[1] recommends obtaining a basal serum tryptase in patients with recurrent, idiopathic, or severe anaphylaxis, and suggests drawing an acute tryptase level during a suspected anaphylactic event with a baseline level drawn at a later time for comparison. Still, analysis of recent evidence suggests that the classic rule that defines mast cell activation with an acute tryptase rise of 20% plus 2 ng/mL above baseline may be imprecise.[21] Although this rule has been validated in perioperative anaphylaxis with an Sn of 98% and Sp of 44%, variability limits the rule. In one analysis, one fourth of individuals with mast cell disorders may exceed this rule with serial measurements alone.[21] As such, alternative thresholds have been proposed based on the index of suspicion, with high Sn (Sn 97.5%; Sp 76.5%) and high Sp (Sp 97.5%; Sn 92.4%) thresholds suggested at acute to baseline serum tryptase ratios of 1.374 for patients in whom clinical suspicion is high and 1.868 suggested when clinical suspicion is low, respectively.[21] A ratio of 1.685 was modeled to have good Sn and Sp, regardless of clinical suspicion (Sn 94.4%, Sp 94.4%), with a tool for evaluation of serum tryptase levels now available.[22]

Because we consider anaphylaxis as a systemic and potentially life-threatening reaction, each set of diagnostic criteria can help to inform our approach.[1] The JTFPP 2023 Anaphylaxis Practice Parameter[1] highlights that meeting any set of anaphylaxis diagnostic criteria is not required in the treatment of a severe allergic reaction and that epinephrine is the first-line treatment for a severe allergic reaction. Conversely, neither use of epinephrine in the treatment of an allergic reaction, nor response to epinephrine, should be used as a surrogate marker for anaphylaxis diagnosis. These are important points, and, as we view the diagnosis of anaphylaxis more globally, our understanding of similarities and differences in anaphylaxis criteria can assist in delivering more nuanced and timely care to patients with severe allergic reactions.[1]

SUBTYPES OF ANAPHYLAXIS

The severity of anaphylaxis is variable across populations but may be more consistent within an individual patient's response to a specific allergen.[1,23–26] Slapnicar *et al*.[23] reported good Fleiss kappa reproducibility scores among 149 patients who presented with recurrent anaphylaxis. Although the allergen threshold is a distinct construct from allergen severity, further studies of food allergy thresholds reinforce the concept that patterns of allergic reactions may be more consistent across short time frames than previously assumed.[24,25] Still, more work is needed to understand the reliability of these patterns, the impact of more diverse allergen triggers, and the durability of patterns over longer time frames.[8,27] Reaction severity in anaphylaxis is impacted by allergen-related factors, patient factors, and treatment, each of which may be variable from reaction to reaction, a fact that may limit confidence in reproducibility of reaction thresholds and severity over time.[1,28]

Anaphylaxis subtypes include persistent (with continued signs or symptoms for at least 4 hours), refractory (characterized by continued anaphylaxis despite three or more doses of epinephrine and symptom-directed therapy), and biphasic (*i.e.,* recurrent anaphylaxis within 48 hours after initial symptom resolution for at least 1 hour and no subsequent allergen exposures) reactions.[1,29] Although refractory anaphylaxis accounts for <0.5% of severe anaphylaxis, it has an outsized impact on mortality (26.2% versus 0.35%).[30,31] Reaction severity is a large driver in the risk of persistent, refractory, and biphasic anaphylaxis, and the optimal management of the most severe refractory cases of anaphylaxis remains a knowledge gap, with

Table 1 **NIAID And WAO side-by-side comparison**

NIAID Criteria (2006)	WAO Criteria (2020)
Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled 1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (*e.g.,* generalized hives; pruritus or flushing; swollen lips, tongue, uvula) and at least one of the following a. Respiratory compromise (*e.g.,* dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) b. Reduced BP or associated symptoms of end-organ dysfunction (*e.g.,* hypotonia [collapse], syncope, incontinence) 2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours) a. Involvement of the skin-mucosal tissue (*e.g.,* generalized hives; itch-flush; swollen lips, tongue, uvula) b. Respiratory compromise (*e.g.,* dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) c. Reduced BP or associated symptoms (*e.g.,* hypotonia [collapse], syncope, incontinence) d. Persistent gastrointestinal symptoms (*e.g.,* crampy abdominal pain, vomiting) 3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours): a. Infants and children: low systolic BP (age specific) or >30% decrease in systolic BP b. Adults: systolic BP of <90 mm Hg or >30% decrease from that person's baseline	Anaphylaxis is highly likely when any one of the following 2 criteria are fulfilled 1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (*e.g.* generalized hives; pruritus or flushing; swollen lips, tongue, uvula) and at least one of the following a. Respiratory compromise (*e.g.,* dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) b. Reduced BP or associated symptoms of end-organ dysfunction (*e.g.,* hypotonia [collapse], syncope, incontinence) c. Severe gastrointestinal symptoms (*e.g.,* severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens 2. Acute onset of hypotension or bronchospasm or laryngeal involvement after exposure to a known or highly probable allergen for that patient (minutes to several hours), even in the absence of typical skin involvement#

NIAID = National Institute of Allergy and Infectious Diseases; WAO = World Allergy Organization; PEF = Peak Expiratory Flow; BP = Blood Pressure.

**Gastrointestinal involvement variably defined as "persistent" (NIAID) or "severe" (WAO). Reproduced with permission from Ref. 1.*

#Acute onset of hypotension or bronchospasm: excluding lower respiratory symptoms triggered by common inhalant allergens or food allergens perceived to cause "inhalational" reaction in the absence of ingestion.

current guidance advising supportive care that includes fluid and pressor support.[32]

The severity of anaphylaxis has been classified by using numerous classification systems. One classification arising from a Delphi expert consensus, published by Dribin *et al.,*[33] advantages careful description of single or multiple organ systems involvement to describe increasing severities of allergic reactions, from mild to life-threatening (grades 1 through 5). This system allows a clear description of reactions to guide treatment, whether or not reactions fulfill any specific criteria for anaphylaxis.[33] This approach can be particularly useful when describing biphasic reactions that may or may not fulfill criteria met during the initial reaction.[29,33] Still, other more simplified approaches to severity grading can be helpful and do not require access to tables necessary for the Dribin system.[33] Perhaps one of the simplest and most easily translatable scoring systems for allergic reactions (anaphylactic and non-anaphylactic) is that of Brown,[34] which describes mild (*e.g.,* cutaneous), moderate (*e.g.,* airway/respiratory, cardiovascular, gastrointestinal involvement), and severe (*e.g.,* hypoxia, hypotension, incontinence, neurologic compromise).[1]

Biphasic anaphylaxis has been reported in up to 20% of patients; however, analysis of more recent evidence suggests that estimates closer to 5% are likely accurate.[7,35] Data from the international anaphylaxis registry, a large cohort that evaluated 8736 patients from 11 countries, described a 4.7% rate of biphasic anaphylaxis.[35] In this study, reaction severity and multiorgan involvement were among the risk factors associated with biphasic reactions.[35] These findings echo those

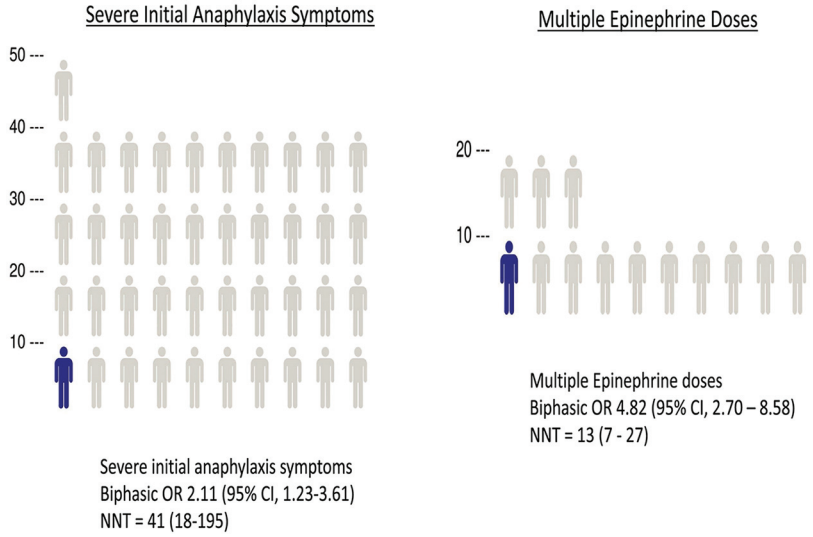

Figure 1. *Reasoned triage and anaphylaxis observation. With reasoned triage, the number needed to treat (observe) to detect biphasic anaphylaxis in a patient with resolved anaphylaxis who received multiple doses of epinephrine was 13 (95% confidence interval [CI], 7–27). Reproduced with permission from Ref. 7.*

of the 2020 JTFPP Anaphylaxis GRADE Guideline,[7] whose systematic review and meta-analysis also described reaction severity (odds ratio 2.11 [95% confidence interval, 1.23–3.61]) and need for multiple doses of epinephrine (odds ratio 4.82 [95% confidence interval, 2.70–8.58]) as significant risks for biphasic reactions (Fig. 1).

ANAPHYLAXIS SEVERITY AND MANAGEMENT

Anaphylaxis severity has important implications in management and prognosis.[1,7,8,24–27] For example, clinicians may consider reasoned triage in the decision for prolonged observation for patients with resolved anaphylaxis, given the associations of anaphylaxis severity, requirement for epinephrine use, and biphasic anaphylaxis.[7] In a health-economic model of management strategies that compared 10,000 patients with resolved anaphylaxis observed for 1 hour with the same number of simulated patients observed for 1–6 hours, routine prolonged observation of all patients cost $68,411 to $230,202 per additional case of with biphasic anaphylaxis observed.[36] With reasoned triage, the number needed to treat (observe) to detect biphasic anaphylaxis in a patient with resolved anaphylaxis who received multiple doses of epinephrine was 13 (95% CI, 7–27) (Fig. 1).[7]

Health-economic analyses have also identified opportunities to increase value of post-anaphylaxis management at home.[13,36–41] In an analysis of reflex use of emergency medical services (EMS) for all patients receiving an epinephrine autoinjector while in the community versus a triaged approach to EMS activation, home monitoring of patients with resolved anaphylaxis was cost-effective (incremental cost-effectiveness ratio for reflex EMS, $142,943,447).[13] Additional value in anaphylaxis management has been suggested in triaged epinephrine autoinjector prescription quantity (favoring a greater number of devices for patients with previous reactions that require epinephrine), use of stock epinephrine devices (*e.g.*, schools and aircraft), and avoiding preemptive use of epinephrine before emergence of symptoms.[37–40] The JTFPP 2023 Anaphylaxis Parameter[1] has considered many of these analyses in formulating preference-sensitive recommendations when appropriate for circumstances characterized by shared decision-making and clinical equipoise. For example, the JTFPP 2023 Anaphylaxis Parameter[1] recommends that clinicians counsel patients at high risk for anaphylaxis to always carry epinephrine but consider single epinephrine devices in circumstances of lower anaphylaxis risk (in jurisdictions where such devices are available), while suggesting in favor of stock-epinephrine programs and a shared decision-making approach in deciding on EMS activation for patients with resolved community anaphylaxis.[41] Key considerations for home observation after use of epinephrine include patient engagement, understanding, adherence, comfort with the approach, access to additional epinephrine, and reaction history.[1,41]

SHARED DECISION-MAKING AND ANAPHYLAXIS

Shared decision-making is an important paradigm of care that touches many aspects of allergy immunology.[42–47] This approach to practice engages patients as experts in their own preferences and values, leveraging patient insights with clinician expertise provided by their health-care professional.[42] Importantly, shared decision-making is appropriate under conditions of equipoise.[48,49] This fact acknowledges that there are often circumstances in which a strong medical recommendation directs a course of action that is highly likely to result in best health (and sometimes health economic) outcomes.[47] Fortunately, contemporary guidelines provide

clear navigational signals for when shared decision-making may be appropriate (*i.e.*, conditional "suggestions") and when clinical circumstances are not preference sensitive (*i.e.*, strong recommendations).[47,50,51] Examples of strong recommendations in the setting of anaphylaxis include consensus-based statement 13 from the 2023 JTFPP Anaphylaxis Practice Parameter,[1] which reinforces the importance of proper preparedness and training with self-injectable epinephrine for patients at high risk for anaphylaxis.

Particularly given the advent of noninjectable routes of epinephrine, the role of preference-sensitive care will likely expand in management of anaphylaxis.[52–54] These options will highlight the need for thoughtful shared decision-making, not just around quantity of self-administered community epinephrine but around the route as well.[14,39,42,47,49,54] As with thresholds for further care, anaphylaxis severity, allergen thresholds, and concomitant therapy will likely influence these decisions.[9,10,21,23,25,26,28,29,33,37,52]

CONCLUSION

Recent progress has been made in our approach to anaphylaxis on several fronts. Key messages include the recognition that fulfilling any set of anaphylaxis diagnostic criteria is not required for epinephrine use in the treatment of a severe allergic reaction. Anaphylaxis is a systemic allergic reaction that can occur across a spectrum of severity. Both NIAID and WAO as well as BCC diagnostic approaches provide some insights and granularity in evaluating patients with severe allergic reactions; however, a unified diagnostic approach would help to simplify management across medical specialties.

Although medicine is complex, when possible, simple messaging can help health-care professionals provide the right care, at the right time, every time.[54] Understanding when and how to leverage a shared decision-making approach to patient management and how this decision relates to recommendation strength can help to facilitate both individualized and timely care. Whereas we look forward to exciting and progressive developments in anaphylaxis in the years to come, by partnering with patients and using guideline-based management paradigms to optimize clinical practice, we can deliver high-value care today.

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