Anaphylaxis: A 2023 Practice Parameter Update

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Contributors: The JTFPP has made a concerted effort to acknowledge all contributors to this parameter. If any contributors have been excluded inadvertently, the JTFPP will ensure that appropriate recognition of such contributions is made subsequently.

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Abbreviations

AAAAI, American Academy of Allergy, Asthma, and Immunology; AAP, American Academy of Pediatrics; ASCIA, Australian Society of Clinical Immunology and Allergy; ACAAI, American College of Allergy, Asthma, and Immunology; ACEI, angiotensin-converting enzyme inhibitor; AIT, allergen immunotherapy; ARB, angiotensin receptor blocker; BB, beta blocker; bST, baseline serum tryptase; CBS, consensus-based statement; CI, confidence interval; CSACI, Canadian Society of Allergy and Clinical Immunology; EAACI, European Academy Allergy and Clinical Immunology; EAI, epinephrine autoinjector; ED, emergency department; EMS, emergency medical services; FAAN, Food Allergy and Anaphylaxis Network; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; HαT, hereditary α-tryptasemia; HCUP, Healthcare Cost and Utilization Project; IA, idiopathic anaphylaxis; IM, intramuscular; IO, intraosseous; JTFPP, Joint Task Force on Practice Parameters; MCAS, mast cell activation syndrome; NIAID, National Institute of Allergy and Infectious Diseases; NMBA, neuromuscular blocking agent; OIT, oral immunotherapy; OJTF, Omalizumab Joint Task Force; POA, perioperative anaphylaxis; PP, practice parameter; RCM, radiocontrast media; REMA, Red Espanola Mastocitosis; SC, subcutaneous; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; TPSAB1, tryptase α/β-1; VIT, venom immunotherapy; WAO, World Allergy Organization.

What's New and What's Different

This practice parameter is not a comprehensive review of anaphylaxis but focuses on 7 areas in which new evidence has emerged and in which recommendations may now be different from previous practice parameters.

Diagnosis. Accurate classification, criteria, and definitions for the diagnosis of anaphylaxis are critical for proper treatment and consistency in research studies that would enable meaningful evidence analysis and stronger recommendations. Revised criteria by the World Allergy Organization (WAO), Brighton, and Delphi Consensus groups aim to create more universally accepted definitions and criteria for anaphylactic reactions. Biphasic anaphylaxis is associated with greater severity of initial reaction, persistent reaction, and more than one dose of epinephrine. Baseline serum tryptase (bST) should be measured in patients presenting with a history of recurrent, idiopathic, or severe anaphylaxis, Hymenoptera venom anaphylaxis, or with suspected mastocytosis. If bST is >8 ng/ml, consider evaluation for hereditary α-tryptasemia (HαT) and clonal mast cell disease. Alpha-gal allergy can be a cause of unexplained anaphylaxis.

Infants and Toddlers. The diagnosis and treatment of anaphylaxis may be even more challenging in infants. As our understanding improves, so can our recommendations for this important age group. In infants and toddlers, patient age is not correlated with reaction severity, and anaphylaxis is unlikely to be the initial reaction to an allergen upon first exposure. Infants and toddlers may display age-specific symptoms that are less often reported in older children and adults.

Community Settings. Anaphylaxis is most difficult to recognize and treat outside of healthcare facilities. Reactions occur at home, school, work, dining out, travelling, or many other locations, and situations can be associated with different patient characteristics, causes, or available options for treatment or prevention. Patients at high-risk for anaphylaxis, and their caregivers, should be counseled regarding carrying and using epinephrine injectors, and recognition and avoidance of exposures. Child-care centers and schools should implement staff training and stock undesignated epinephrine autoinjectors (EAI) that can be used to treat any individual who experiences anaphylaxis.

Epinephrine Autoinjectors. The cardinal treatment of anaphylaxis is prompt epinephrine injection. The optimal prescribing and use of EAI devices requires specific counseling and training of patients and caregivers, including when and how to administer the EAI, and whether and when to call 911. Healthcare professionals should consider a patient's risk factors for severe anaphylaxis, their values and preferences, and the burden of both anaphylaxis and EAI prescription when deciding whether to prescribe EAIs and how many EAIs to prescribe. If epinephrine is used promptly, immediate activation of emergency medical services (EMS) may not be required if the patient experiences prompt, complete, and durable response to treatment. EMS should be activated if anaphylaxis is severe, fails to resolve promptly, fails to resolve completely or nearly completely, or returns or worsens following a first dose of epinephrine.

Beta-blockers (BB) and ACE inhibitors (ACEI). Both BB and ACEI have been previously considered to be contraindicated in patients at high-risk for anaphylaxis

because of increased risk of severe anaphylaxis. Larger and more focused studies have provided new insights into the relative risk of these medications and have improved guidance on whether it is necessary to change or stop these medicines in some patients. For most medical indications, the risk of stopping or changing the medication may exceed the risk of more severe anaphylaxis if the medication is continued, especially in patients with insect sing anaphylaxis. Venom immunotherapy (VIT) may be considered for patients receiving BB/ACEI, with shared decision-making regarding the balance of benefits and harms. Patients receiving maintenance dose allergen immunotherapy (AIT) have minimal increased absolute risk of severe anaphylactic reaction when receiving BB/ACEI and may consider continuing AIT and medications based on shared decision-making.

Mast Cell Disorders. Many mast cell disorders are associated with an inherently greater risk of anaphylaxis. Advances in recent years are beginning to enable better recognition of the related phenotypes, application of new diagnostic methods, and targeting treatment to prevent anaphylaxis. Baseline serum tryptase should be measured in patients with severe insect sting anaphylaxis, particularly among those who had hypotension and/or absence of urticaria, in all cases of recurrent unexplained anaphylaxis, and in patients with suspected mastocytosis. Evaluation for mastocytosis, including a bone marrow biopsy, should be considered for adult patients with severe insect sting anaphylaxis or recurrent idiopathic anaphylaxis (IA), particularly those with a predictive Red Espanola MAstocitosis (REMA) score. New treatment modalities are under investigation to prevent anaphylaxis in high-risk patients.

Peri-operative anaphylaxis (POA). Continued study of anaphylaxis during and after surgical anesthesia has improved recognition of the most common culprits and the approach to counseling for future surgery and anesthesia through testing, challenge, or strategic avoidance, when necessary, based on availability of the materials and expertise. After POA, repeat anesthesia may proceed in the context of shared decision-making and directed by history and results of diagnostic evaluation. Immediate hypersensitivity skin testing (percutaneous and intradermal), and/or in vitro specific-IgE testing should be performed to all potential pharmacologic and non-pharmacologic

culprits used during the perioperative period, as well as to available alternatives for anesthesia at the healthcare facility. Challenges should be performed to all culprit agents to which skin and/or in vitro testing is negative, but if this is not feasible, avoidance of culprit pharmacologic and non-pharmacologic agents associated with POA may be considered if equally efficacious, structurally-unrelated alternatives are available.

Executive Summary

Anaphylaxis is characterized as a life-threatening systemic allergic reaction that can include a range of clinical signs and symptoms. Most definitions of anaphylaxis include vague words such as “generalized” and/or “systemic” and/or “multi-organ” but there are instances where a single system is primarily affected. While anaphylaxis is not an infrequent occurrence, with a lifetime prevalence estimated at 1.6-5.1%, advancing the understanding of anaphylaxis has been hindered by the fact that several anaphylaxis criteria and grading systems exist, which can result in differing clinical assessments and renders comparisons between research studies difficult. Having consistency in diagnosis and classification of anaphylaxis is critical for proper treatment and to facilitate research efforts. The 2006 National Institute of Allergy and Infectious Diseases (NIAID) and Food Allergy and Anaphylaxis Network (FAAN) defined anaphylaxis as one of several clinical diagnostic scenarios. This set of criteria has been widely adopted and validated. The 2007 Brighton Collaboration Anaphylaxis Working Group created a definition specifically for anaphylaxis occurring as an adverse event following an immunization. In an effort to further simplify diagnosis, the WAO created a definition with only two criteria. Recognizing that anaphylaxis courses can be variable, a Delphi Consensus group defined parameters for biphasic, persistent, and refractory anaphylaxis. Validation of the WAO criteria and Delphi Consensus group definitions will be helpful in determining their clinical utility.

Having reliable predictors of anaphylaxis severity can help optimize treatment, but severity of reactions is influenced by many different factors related to the patient and the allergen. Identified risk factors for severe anaphylaxis include the symptoms of hypotension and hypoxemia, as well as patient factors of older age and pre-existing lung disease and drug allergen as the trigger. Biphasic anaphylaxis is associated with greater severity of the initial reaction and requirement of more than one dose of epinephrine to treat the initial symptoms. While determining the diagnosis and severity grading are not necessary for initiating treatment with epinephrine during an acute allergic reaction, establishing the anaphylaxis diagnosis and severity using available criteria and grading systems is important to communicate the clinical history and to

counsel on future management. Conversely, the use of epinephrine to treat an allergic reaction does not confer a diagnosis of anaphylaxis.

Understanding anaphylaxis relies on a thorough clinical history that includes patient characteristics (age, gender, medical and atopic history, concurrent medications), detailed description of the reaction (possible triggers, symptom pattern, timing of onset duration of symptoms), concomitant factors (e.g., exercise, viral infection, medications, menstrual status, stress, food, alcohol), and response to treatment. The diagnosis can be supported by an elevated acute serum tryptase level. Although a tryptase level above the lab-defined normal value (e.g., > 11.4 ng/ml in many labs) is informative, some cases of anaphylaxis may not be associated with a tryptase elevation to that level. Particularly in these situations, an acute serum total tryptase level at least 20% plus 2 ng/ml over the patient's bST level may provide evidence of systemic mast cell activation.

For patients with a history of recurrent, idiopathic, or severe anaphylaxis, or with suspected mastocytosis, obtaining a bST level is advisable as elevated levels are seen in patients with HαT and clonal mast cell disease and are associated with more severe anaphylaxis. Adult patients with severe insect sting anaphylaxis or recurrent IA may require evaluation for mastocytosis, including a bone marrow biopsy, especially if they have a predictive REMA score. Alpha-gal allergy should be considered in patients who have recurrent IA and an appropriate exposure history.

Infant anaphylaxis

With implementation of food allergy prevention guidelines, there has been increased awareness and understanding of anaphylaxis in the infant/toddler age group. Diagnosing anaphylaxis in infants and toddlers can be challenging, and there are no age-specific anaphylaxis diagnostic criteria. Therefore, the current NIAID/FAAN or WAO anaphylaxis criteria should be used to establish the diagnosis of anaphylaxis in infants/toddlers. These young children are unable to communicate their subjective symptoms to their caregivers, and many signs and symptoms of anaphylaxis can be indistinguishable from normal infant behaviors or can be attributable to other conditions, so recognizing these symptoms as part of anaphylaxis requires astute clinical skills. In

this young age group, patient age is not correlated with reaction severity, and anaphylaxis is unlikely to be the initial reaction to an allergen upon first exposure. Clinicians may prescribe either the 0.1 mg or the 0.15 mg EAI dose for infants/toddlers weighing less than 15 kg. Additional research is needed to address knowledge gaps in the epidemiology, classification, diagnosis, and management of anaphylaxis in infants and toddlers.

Anaphylaxis in the Community Setting

Anaphylaxis is not always easy to recognize, and anaphylaxis occurring outside the medical setting can be particularly challenging to manage. Most cases occur at home, but anaphylaxis has also been reported in community settings, including school, work, while dining out, and during travel. Given the unpredictability of anaphylaxis, at-risk patients and their caregivers should be counseled on allergen avoidance strategies, identification of signs and symptoms of allergic reactions, and advised to be prepared with EAIs at all times. Implementation of staff training and stocking undesignated EAIs at child-care centers and schools may help improve anaphylaxis management in these locations. Whereas current research does not support consistent benefits of site-wide food specific prohibition in the management of food allergies in child-care centers and schools, there may be specific circumstances in which implementation of allergen-restricted zones (e.g., milk-free table) may be appropriate, such as when there are students who lack the capacity to self-manage.

Patient counseling on strategies to minimize allergen exposure and preparedness to manage allergic reactions while dining out, during travel, or activities in any community setting is important because anaphylaxis can occur anywhere. Given that the risk of a severe food allergy reaction is primarily associated with ingestion of a food allergen rather than skin contact or inhalation, steps to prevent unintentional allergen ingestion should be the main priority for these patients. Counseling should include discussions on US labeling regulations that require disclosure of major allergens on labels of prepackaged foods, while also noting that restaurants are not required to declare ingredients or provide allergy warnings for non-prepackaged foods.

Management of anaphylaxis risk is a “shared responsibility” in the restaurant setting (i.e., both the allergic diner and food service staff have roles to play in keeping the diner safe), so clear communication is essential. There is a lack of high-quality data on the effects of specific strategies for safe dining, but patients may consider reviewing menu options to make informed choices, disclosing the allergy to a knowledgeable and responsible food service staff member prior to ordering their meal, inform dining companions of the food allergy, and avoiding situations where there may be a higher risk of cross-contact, such as buffets.

Clinicians should counsel patients on standard management practices for allergic reactions, including having epinephrine readily available. While airplane emergency kits in the US contain epinephrine vials, drawing up appropriate doses using a needle and syringe in a cramped air cabin mid-flight during an acute reaction is challenging and could lead to delayed treatment. Importantly, stock epinephrine is not available in airports or during transit between travel destinations so it is imperative that patients are prepared with their own EAIs at all times.

Epinephrine Autoinjectors

Epinephrine is the first line treatment for anaphylaxis, and EAIs allow patients to have this emergency medication available outside the medical setting. A patient’s risk factors for severe anaphylaxis, their values and preferences, and the burden of both anaphylaxis and EAI prescription are important factors to consider when deciding whether to prescribe EAIs and how many EAIs to prescribe. There are no validated risk-stratification algorithms in the research literature to guide EAI prescription, but expert opinion suggests that patients with the following are at higher likelihood of requiring treatment with their prescribed EAI: history of systemic allergic reaction or anaphylaxis to their food allergen; frequent allergen exposure through occupation or other activities (for venom, latex, drug allergy); prior systemic allergic reaction to AIT or VIT; venom allergy with honeybee as the trigger, elevated bST level, older age, underlying cardiovascular disease, venom-induced anaphylaxis not treated with VIT; exercise-induced anaphylaxis; and cold-induced urticaria. Prescription of EAIs is advised for omalizumab and sublingual immunotherapy (SLIT) even though they cause anaphylaxis

in <1% of all treated patients. Multiple EAIs are commercially available so dosage, needle length, affordability, access, and patient treatment preferences should be taken into account when prescribing EAIs.

The current standard practice is to treat anaphylaxis with a dosage of epinephrine of 0.01 mg/kg, up to a maximum of 0.3 mg for children and teenagers and 0.5 mg for adults. EAIs are only available in a limited number of premeasured doses. While the US FDA has approved 0.3 mg EAIs for patients weighing ≥30 kg, 0.15 mg EAIs for patients weighing 15–30 kg, and a 0.1 mg EAI (Auvi-Q) for patients weighing 7.5–15 kg, multiple medical organizations (AAAAI, American Academy of Pediatrics [AAP], Canadian Society of Allergy and Clinical Immunology [CSACI], and European Academy Allergy and Clinical Immunology [EAACI]) support switching to 0.3 mg at 25 kg to limit underdosing in patients nearing 30 kg. The 0.1 mg EAI is not universally available, and the AAP and JTFPP support the use of 0.15 mg EAIs for young children less than 15 kg.

Those prescribed EAIs should receive counseling and training on when and how to administer the device and steps to take after administration. Available evidence suggests that early epinephrine use for anaphylaxis may help improve clinical outcomes by decreasing risk of biphasic reactions and the need for hospitalization. Therefore, epinephrine should be administered at the first sign of suspected anaphylaxis. However, there is no evidence that pre-emptive use of epinephrine in an asymptomatic patient will prevent anaphylaxis. Serious adverse reactions to intramuscular (IM) epinephrine are rare and should not pose a barrier to the prescription or early administration of EAIs when indicated. Immediate activation of EMS after EAI use may not be required if the patient experiences prompt, complete, and durable response to treatment and has access to addition EAIs. Situations that would warrant EMS activation include severe anaphylaxis, symptoms do not resolve promptly, completely or nearly completely, or symptoms return or worsen.

Beta-blockers (BB) and ACE inhibitors (ACEI)

Both BB and ACEI have been previously considered to be contraindicated in patients at high-risk for anaphylaxis because their physiologic effects could theoretically

increase the severity of anaphylaxis and impact the response to treatment. BB may reduce compensatory cardiovascular responses to anaphylaxis, enhance the release of mast cell mediators, and interfere with the effects of epinephrine. ACEIs prevent the breakdown of bradykinin, promote vasodilation, and may have direct effects on mast cells.

With more recent data and availability of more cardio-selective beta-blocking agents, shared decision-making is needed when assessing the risks of potential anaphylaxis while receiving the BB/ACEI, the cardiac risk of stopping the BB/ACEI, and alternative medications or procedures. For patients with insect sting allergy who receive BB/ACEI, VIT may be considered as there does not appear to be any increased risk of reaction to VIT associated with these cardiovascular medications. Similarly, AIT may be pursued in patients on BB or ACEI, but shared decision-making (regarding the potential risk of a more severe reaction) is important when considering this treatment approach. Those on maintenance AIT have minimal increased risk of severe anaphylactic reaction when concurrently on BB/ACEI. For planned procedures that carry a risk of anaphylaxis (eg, radiocontrast media [RCM], challenge/ desensitization, and infusion), if the BB/ACEI cannot be safely interrupted, then shared decision-making is critical to weigh the medical necessity of the procedure against the relative risk of anaphylaxis and the possibility of more severe reaction if the BB/ACEI is continued. Patients at significant risk for recurrent and unexpected anaphylaxis (eg, severe food allergy, mastocytosis or MCAS, or recurrent IA) should receive counseling about the theoretical risk of more severe anaphylaxis, and should avoid non-selective BB or ACEI, if possible. There is not sufficient evidence to distinguish ARBs from ACEIs with regard to the potential risk of more severe anaphylaxis.

Mastocytosis

Mastocytosis is a clonal disorder of mast cell proliferation and is associated with episodic and chronic mast cell activation symptoms, including anaphylaxis. An estimated 40-50% of adults and 10% of children with mastocytosis are at risk for anaphylaxis. Risk factors for anaphylaxis associated with mastocytosis have been

identified as male gender, total serum IgE >15 kU/L, atopic background, and tryptase levels less than 42 ng/mL.

The World Health Organization has updated classification and diagnostic criteria for cutaneous and systemic mastocytosis. Key presenting symptoms of systemic mastocytosis will overlap with anaphylaxis but also may include the cutaneous symptoms (eg, urticaria pigmentosa, blisters or bullae in infants, pruritus, urticaria, and flushing), pre-syncope/syncope, constitutional symptoms (eg, fevers, weight loss, night sweats), bone pain, and prominent gastrointestinal symptoms like reflux, nausea, vomiting, diarrhea, and colic. On physical exam, hepatosplenomegaly and lymphadenopathy may be prominent especially in patients with advanced disease. While an elevated bST level (>20 ng/mL) is considered a significant contributory finding to the diagnosis, a tryptase elevation in isolation is insufficient to make the diagnosis as this marker is not specific for a mast cell disorder. A bone marrow biopsy revealing at least 15 mast cells in aggregates is the major diagnostic criterion for diagnosis of systemic mastocytosis. Clinicians ordering a bone marrow biopsy should ask for staining for tryptase, CD25 immunohistochemistry and flow cytometry, the KIT D816Vmutation using a highly sensitive allele specific PCR based technique, and if there is peripheral eosinophilia, a FIP1L1-PDGRA mutational analysis.

There should be a high index of suspicion for mastocytosis in patients who have had severe insect sting anaphylaxis, particularly among those who had hypotension and/or absence of urticaria, and for patients with recurrent unexplained/IA. Recent studies suggest that in patients with insect sting anaphylaxis of any severity, bST levels greater than 8 ng/ml indicate increased risk of severe anaphylaxis to stings and evaluation for an underlying mast cell disorder (including HαT) may be warranted. Treatment with VIT reduces the frequency and severity of reactions to stings in patients with mastocytosis, but these patients have higher rates of systemic reactions to VIT injections (15% compared with 5% of patients on VIT who do not have mastocytosis). Patients with mastocytosis who have discontinued VIT (even after a 5 year course) remain at higher risk of relapse; therefore, these patients should continue VIT indefinitely.

For patients with mastocytosis and recurrent anaphylaxis despite optimized prophylactic therapy with H1 and H2 antihistamines, off-label treatment with omalizumab can be considered as studies report it provided improved control of symptoms and prevention of anaphylaxis. There is also evidence that mast cell cytoreduction results in improvement of anaphylaxis in mastocytosis.

Perioperative anaphylaxis (POA)

Perioperative anaphylaxis, which has a greater risk of death than other forms of anaphylaxis, occurs at a rate of 15.3 per 100,000 cases. Evaluation of POA is complicated by the fact that multiple agents are usually administered simultaneously or in close succession. Studies suggest that antibiotics and paralytics (neuromuscular blocking agents [NMBA]) are the more common culprits. Rigorous evidence on this topic is lacking due to the limitations resulting from the relatively rare occurrence of POA and inability to perform double-blind studies because of ethical considerations. Therefore, the strength of evidence is uniformly low to very low.

After POA, repeat anesthesia may proceed in the context of shared decision-making and directed by history and results of diagnostic evaluation. Immediate hypersensitivity skin testing (percutaneous and intradermal) and/or in vitro specific-IgE testing should be performed to all potential pharmacologic and non-pharmacologic culprits used during the perioperative period, as well as to alternatives for anesthesia at the healthcare facility. Published resources provide empirical, non-irritating concentrations for hypersensitivity skin testing of potential culprit pharmacologic causes of POA. However, availability of drugs for testing is limited by the controlled nature of many agents, and positive and negative likelihood ratios of such testing have not been determined. Delaying immediate hypersensitivity skin testing for 4-6 weeks following anaphylaxis is generally recommended since a “refractory period” may result in lack of skin testing response. Data demonstrate that graded challenge of agents with negative test results can proceed safely, though this procedure may require coordination with an anesthesiologist, depending on the medication tested. If testing and challenge are not feasible, avoidance of culprit pharmacologic and non-pharmacologic agents associated

561 with POA may be considered if equally efficacious, structurally-unrelated alternatives
562 are available.

Methods and overview of the practice parameter development process

The purpose of this practice parameter is to evaluate current evidence and provide guidance to healthcare practitioners on the diagnosis and management of anaphylaxis. This updated practice parameter focuses on topics selected by the workgroup as described below. By identifying knowledge gaps in the research literature, these guidelines may also help researchers direct attention to topics on which more studies are needed. This practice parameter is meant to update the selected topics and to complement our previous practice parameters on anaphylaxis[1, 2] but does not entirely replace or supersede those documents which may be consulted for additional background discussion on anaphylaxis and for guidance on topics not selected for review in the current update.

Evidence has evolved since the previous anaphylaxis practice parameters.[1, 2] Although the ideal type of reference would consist of a randomized, double-blind, placebo-controlled study, the topic of this practice parameter is represented by very few such studies. Consequently, it was necessary to use observational studies, case series, basic laboratory reports, and expert review articles to develop a document that addresses most of the issues included in this practice parameter. The references cited in this practice parameter represent the best quality and most relevant evidence for the discussion and recommendations made herein.

Development of these guidelines was funded by the JTFPP, which is financially supported by the ACAAI and AAAAI. Leadership from the ACAAI and AAAAI reviewed and approved the topics and questions for this document after input from the JTFPP and the Anaphylaxis workgroup. Members of the JTFPP and Anaphylaxis workgroup received no compensation for their work related to this practice parameter. The practice parameter development process involved several stages. A workgroup of experts was appointed by the JTFPP on behalf of the AAAAI and ACAAI. The workgroup, co-chaired by David Golden, MD and Julie Wang, MD, developed a list of key clinical questions and topics to be addressed. The topics and questions were selected to reflect the most

significant advances and changes in the field that affect clinical practice. At least 3 workgroup members were assigned to review and write each topic. They then performed literature searches to determine the most up to date information for each consensus-based statement (CBS) and discussion. Searches of the medical literature were performed using a variety of terms that were considered relevant for the topics under review in this practice parameter. Literature searches were performed on PubMed, and in some cases also on MEDLINE, Medscape, Google Scholar, and the Cochrane Database of Systematic Reviews. The time frame for most searches was 2015-2022, but some topics required searches for an expanded time frame from 1960 to the present. The searches included only English-language articles. The draft topics were reviewed by the workgroup co-chairs with subsequent revision by the authors. Subsequently, all sections were reviewed and revised by the entire workgroup through several rounds of electronic and teleconference reviews. The practice parameter was then reviewed in detail by the JTFPP and revisions, when needed, were made in conjunction with the workgroup. External review followed as described above under ‘‘resolving conflict of interest’’ in the Front Matter.

This practice parameter contains recommendations intended to optimize care of patients and to assist physicians and/or other healthcare practitioners and patients to make decisions regarding evaluation and management of suspected anaphylaxis. This practice parameter was not intended to be a document employing Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology. Because GRADE documents require a comprehensive literature search, systematic review, and meta-analysis for each question, it is beyond the scope and resources of a traditional practice parameter to attempt to conduct a GRADE analysis for the large number of the questions for which clinicians would like an answer. In addition, for many questions, there is very limited evidence, and the workgroup/JTFPP must rely on expert evidence and opinion. Therefore, in this practice parameter most recommendations are made as CBSs, which are based on a recent literature search of PubMed to update or add to the 2015 and 2020 Anaphylaxis practice parameter documents.[1, 2] For the non-GRADE CBSs, the terminology used is intended to be transparent and consistent with descriptions used across JTFPP Traditional and GRADE guidelines. However, the use

of this terminology does not imply that we are equating our recommendations to the rigor required in a GRADE guideline.

The strength of each CBS is determined to be either strong or conditional based on published evidence, expert evidence, and expert opinion. The significance and implications of this rating are described in **Table I**. Although the terminology is modeled after the GRADE format, the rigor of the evidence collection and analysis is limited. The certainty of evidence for each recommendation is determined to be high, moderate, low, or very low based on the kind of evidence that has been published (e.g., randomized controlled trials, observational studies, case series and reports) and factors that downgrade or upgrade the certainty of the evidence. The significance and implications of this rating are described in **Table II**. The intended implications of these statements are similar to the GRADE format but the evidence basis is not necessarily as conclusive. When the JTFPP did not have adequate published evidence with which to make a recommendation, but nonetheless recognized the need to provide guidance to the clinician, the CBSs were based on the collective expert opinion and experience of the workgroup and JTFPP. **Table III** lists all the recommendations.

Table I. Grading the strength of recommendations[3]

Strong Recommendation

The workgroup and JTFPP are confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects. This recommendation may be appropriate to be used as a practice standard indicator. When making a strong recommendation, the wording is “We recommend” implying that the clinician would choose to follow the recommendation in most circumstances.

The implications of a **strong recommendation** are:

- For patients—most people in your situation would want the recommended course of action and only a small proportion would not; request discussion if the intervention is not offered

- For clinicians—most patients should receive the recommended course of action
- For policy makers—the recommendation can be adopted as a policy in most situations

Conditional Recommendation

The workgroup and JTFPP concluded that the desirable effects of adherence to a recommendation probably outweigh the undesirable effect but are not confident. When making a conditional recommendation, the wording is "We suggest" implying that the clinician may choose to follow the recommendation but that decisions may vary based on contextual factors.

The implications of a **conditional recommendation** are:

- For patients—most people in your situation would want the recommended course of action, but many would not
- For clinicians—you should recognize that different choices will be appropriate for different patients and that you must help each patient to arrive at a management decision consistent with their values and preferences. It is likely that shared decision-making will play a major role in arriving at the management decision.
- For policy makers—policy making will require substantial debate and involvement of many stakeholders

640 **Table II. Grading the certainty of evidence for each recommendation.[4]**

High = Further research is very unlikely to change our confidence in the estimate of effect. The recommendation is based on high quality evidence, e.g., multiple highly rated randomized controlled trials, systematic reviews and meta-analyses

Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. The recommendation would

likely be based upon somewhat limited evidence, e.g., reduced number or quality of randomized controlled trials, controlled trials without randomization

Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. The recommendation would likely be based upon very weak evidence, e.g., non-experimental studies, registries, comparative studies

Very low = Any estimate of effect is very uncertain. The recommendation is based largely on very low quality studies and/or on expert opinion.

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List of Recommendations

Table III. List of recommendations.

Section and Number	Method	Recommendation	Strength of Recommendation	Certainty of Evidence
Diagnosis of anaphylaxis				
1	CBS	We recommend obtaining a bST in patients presenting with a history of recurrent, idiopathic, or severe anaphylaxis, particularly those presenting with hypotension.	Strong	Moderate
2	CBS	We suggest drawing an acute phase tryptase level as early as possible during a suspected anaphylactic event (ideally within 2 hours after onset of symptoms). A second (baseline) tryptase measurement should be drawn at a later time for comparison to determine if there was a significant elevation.	Conditional	Moderate
3	CBS	We suggest clinicians consider evaluation for HαT in patients with elevated bST (greater than 8 ng/mL).	Conditional	Low
4	CBS	We suggest clinicians consider evaluation for mastocytosis, including a bone marrow biopsy, for adult patients with severe insect sting anaphylaxis or recurrent IA, particularly those with a predictive REMA score.	Conditional	Moderate
5	CBS	We suggest that clinicians consider alpha-gal allergy as a possible cause of	Conditional	Moderate

		recurrent IA in a patient with history of possible tick bite; when appropriate, check an alpha-gal IgE, and advise a trial elimination of mammalian meat if alpha-gal IgE sensitization is detected.		
6	CBS	We suggest that meeting diagnostic criteria for anaphylaxis is not required prior to the use of epinephrine.	Conditional	Very low
7	CBS	We suggest that neither the clinical decision to administer epinephrine, nor the clinical response to epinephrine, be used as a surrogate marker to establish a diagnosis of anaphylaxis.	Conditional	Very low
Anaphylaxis in infants and toddlers				
8	CBS	We suggest clinicians use current NIAID/FAAN or WAO anaphylaxis criteria to assist in the diagnosis of anaphylaxis in infants/toddlers, since there are no criteria specific to this age group.	Conditional	Low
9	CBS	We suggest clinicians be aware that, in infants and toddlers, patient age is not correlated with reaction severity.	Conditional	Very low
10	CBS	We suggest clinicians be aware that anaphylaxis is unlikely to be the initial reaction to a food or medication upon first exposure.	Conditional	Low
11	CBS	We suggest clinicians be aware that parents of infants and toddlers may report age-specific symptoms that are less	Conditional	Very low

		often reported by older children and adults.		
12	CBS	We suggest clinicians prescribe either the 0.1 mg or the 0.15 mg EAI dose for infants/toddlers weighing less than 15 kg.	Conditional	Low
Anaphylaxis in community settings				
13	CBS	We recommend clinicians counsel patients at high-risk of anaphylaxis to always carry self-injectable epinephrine and teach patients proper indications and use.	Strong	Very low
14	CBS	We recommend clinicians educate patients on avoidance of potential exposure to their allergen(s).	Strong	Very low
15	CBS	We recommend clinicians educate patients that the main route of food-induced anaphylaxis is by ingestion and not contact or inhalation.	Strong	Moderate
16	GRADE	We suggest child-care centers and schools implement staff training for allergy and anaphylaxis management.	Conditional	Very low
17	GRADE	We suggest that child-care centers and schools not implement site-wide food specific prohibition, because current research does not support consistent benefits. Special circumstances: It might be appropriate to implement allergen-restricted zones (eg, milk-free table) when there are students who lack the capacity to self-manage.	Conditional	Very low
18	GRADE	We suggest that child-care centers and schools stock	Conditional	Very low

		undesignated EAIs that can be used to treat any individual on school grounds who experiences anaphylaxis.		
19	CBS	We suggest clinicians counsel patients that although US regulations require disclosure of major allergens on labels of prepackaged foods, restaurants are not required to declare ingredients or provide allergy warnings for non-prepackaged foods.	Conditional	Very low
20	CBS	We suggest clinicians counsel patients on safe practices for dining outside of the home.	Conditional	Very low
21	CBS	We suggest that advising individuals at risk of anaphylaxis to wear or carry medical identification (e.g., jewelry or wallet card) be considered optional. If worn or carried, the wording on medical alert jewelry or wallet cards should be verified for accuracy by a healthcare professional.	Conditional	Very low
22	CBS	We suggest that keeping stock epinephrine in community settings should be encouraged, if feasible.	Conditional	Very low
Epinephrine autoinjectors: when and how to prescribe				
23	CBS	We recommend clinicians routinely prescribe EAIs to patients at higher risk of anaphylaxis. When deciding whether to prescribe EAIs to lower risk patients, we suggest that clinicians engage in a shared decision-making process that considers the patients'	Conditional	Very low

		risk factors, values, and preferences.		
24	CBS	We suggest that clinicians consider a patient's risk factors for severe anaphylaxis, their values and preferences, and contextual factors when deciding whether to prescribe only one versus multiple EAIs. We suggest they routinely prescribe more than one EAI when patients have previously required multiple doses of epinephrine to treat an episode of anaphylaxis and/or have a history of biphasic reactions.	Conditional	Very low
25	CBS	We suggest that clinicians counsel patients and caregivers to give epinephrine at the first sign of suspected anaphylaxis. We suggest that, in general, clinicians counsel patients or caregivers to not give epinephrine pre-emptively to an asymptomatic patient.	Conditional	Very low
26	CBS	We suggest that clinicians counsel patients that immediate activation of EMS may not be required if the patient experiences prompt, complete, and durable response to treatment with epinephrine, provided that additional epinephrine and medical care are readily available, if needed. We suggest that clinicians counsel patients to always activate EMS following epinephrine use, if anaphylaxis is severe, fails to resolve promptly, fails to	Conditional	Very low

		resolve completely or nearly completely, or returns or worsens following a first dose of epinephrine.		
27	CBS	Serious adverse reactions to IM epinephrine are very rare and should not pose a barrier to the prescription or early administration of EAIs when indicated. To manage the risk of adverse events, we recommend that clinicians counsel patients and caregivers on the proper use of EAIs, the common side effects, and the need for immediate evaluation and treatment when signs or symptoms of serious adverse events develop.	Strong	Low
28	CBS	We suggest that clinicians discuss the potential financial and psychosocial burdens of EAIs with patients while engaging in shared decision-making.	Conditional	Very low
29	CBS	When deciding which EAI to prescribe, we suggest that clinicians consider dosage, needle length, affordability, access, and patient treatment preferences.	Conditional	Very low
30	CBS	During visits with patients who have been prescribed EAIs, we recommend that clinicians routinely review the essentials of EAI carriage, storage, and use; encourage patients to regularly practice EAI administration with a trainer device; and discuss strategies to manage barriers to adherence that	Strong	Low

		patients may have experienced.		
Beta blocker and angiotensin converting enzyme inhibitor medications				
31	CBS	We suggest that patients with a history of insect sting anaphylaxis who are not on VIT should continue BB or ACEI when the medical necessity of the daily medication outweighs the chance of increased severity of anaphylaxis to a sting.	Conditional	Low
32	CBS	We suggest that VIT should be recommended to patients with a history of insect sting anaphylaxis who are treated with BB or ACEI, with shared decision-making regarding the potential benefits and harms of concurrent VIT treatment and medication, compared to withholding either the treatment or the medication.	Conditional	Low
33	CBS	We suggest in most cases, treatment with BB or ACEI should not be changed or discontinued in patients receiving maintenance VIT.	Conditional	Moderate
34	CBS	We suggest use of initial AIT may be considered in patients who are treated with BB or ACEI, with shared decision-making. It would be preferable to replace the BB or ACEI, if there is an equally safe and effective alternative.	Conditional	Low
35	CBS	We suggest that patients receiving maintenance dose AIT have minimal increased risk of severe anaphylactic reaction when on BB/ACEI and may consider	Conditional	Low

		continuing AIT and medications based on shared decision-making.		
36	CBS	For planned procedures (e.g., RCM, challenge/desensitization, and infusion) if the BB/ACEI cannot be safely interrupted, we suggest shared decision-making discussion of the medical necessity (benefit) of the procedure, the relative risk of anaphylaxis, the possibility of more severe reaction if the medication is continued, and the risk of stopping the medication.	Conditional	Very low
37	CBS	We suggest that all patients at significant risk for recurrent and unexpected anaphylaxis (e.g., those with confirmed severe food allergy, those with mastocytosis or MCAS, or with recurrent IA) should be counseled about the theoretical risk of more severe anaphylaxis, and should avoid, where possible, the use of non-selective BB or ACEI.	Conditional	Moderate
Mastoycytosis and anaphylaxis				
38	CBS	We recommend clinicians should order a bone marrow biopsy with staining for tryptase, CD25 immunohistochemistry and flow cytometry, and the KIT D816V mutation when there is strong suspicion for systemic mastocytosis.	Strong	Moderate
39	CBS	We recommend clinicians should not rely on serum tryptase levels alone for diagnostic assessment of	Strong	Moderate

		the likelihood that a patient does or does not have a clonal mast cell disorder.		
40	CBS	We recommend measurement of bST in: patients with severe insect sting anaphylaxis, particularly those who had hypotension and/or absence of urticaria; in all cases of recurrent unexplained anaphylaxis; and in patients with suspected mastocytosis.	Strong	Moderate
41	CBS	We suggest clinicians consider evaluation for mastocytosis, including a bone marrow biopsy, for adult patients with severe insect sting anaphylaxis or recurrent IA, particularly those with a predictive REMA score.	Conditional	Moderate
42	CBS	We suggest VIT in patients with mastocytosis and insect sting anaphylaxis should be continued indefinitely in such patients due to the increased risk of severe or fatal sting anaphylaxis if VIT is discontinued.	Conditional	Low
Perioperative anaphylaxis				
43	CBS	We suggest that immediate hypersensitivity skin testing (percutaneous and intradermal) and/or in vitro specific-IgE testing should be performed, when available, to all potential pharmacologic and non-pharmacologic culprits used during the perioperative period.	Conditional	Very low
44	CBS	We suggest that immediate hypersensitivity testing to	Conditional	Very low

		suspected culprit (and alternative) agents should be delayed after POA, unless repeat surgery cannot be postponed. If surgery with general anesthesia is needed sooner, then testing should be performed as soon as possible.		
45	CBS	We suggest that challenges should be performed to all culprit agents to which skin and/or in vitro testing is negative.	Conditional	Very low
46	CBS	We suggest that repeat anesthesia may proceed in the context of shared decision-making and as directed by history and results of diagnostic evaluation.	Conditional	Low
47	CBS	We suggest that avoidance of culprit pharmacologic and non-pharmacologic agents associated with POA may be considered, regardless of test results if challenge is not feasible and equally efficacious, structurally-unrelated alternatives are available.	Conditional	Low
48	CBS	We offer no recommendation for or against the use of pretreatment prior to return to the operating room in patients with negative cutaneous (percutaneous and intradermal) and/or in vitro specific-IgE testing (and challenge when possible) to all suspected POA culprit agents.	None	Very low

644 ACEI, angiotensin-converting enzyme inhibitor; AIT, allergen immunotherapy; BB, beta blocker; bST,
645 baseline serum tryptase; CBS, consensus-based statement; EAI, epinephrine autoinjector; EMS,
646 emergency medical services; FAAN, Food Allergy and Anaphylaxis Network; HαT, hereditary α-

tryptasemia; IA, idiopathic anaphylaxis; IM, intramuscular; MCAS, mast cell activation syndrome; NIAID, National Institute of Allergy and Infectious Disease; POA, perioperative anaphylaxis; RCM, radiocontrast media; REMA, Red Espanola Mastocitosis; VIT, venom immunotherapy; WAO, World Allergy Organization.

MAIN TEXT

Introduction and Background

Our understanding of anaphylaxis has grown steadily in recent years, but many important knowledge gaps remain.[5] The previous traditional practice parameter published in 2015 focused on the definition of anaphylaxis, prescribing of EAIs, mast cell disorders, and unusual manifestations of anaphylaxis.[1] It also provided updates on the evaluation, management, and prevention of anaphylaxis, and anaphylaxis to foods, drugs, biologicals, insect stings, seminal fluid, exercise, subcutaneous immunotherapy (SCIT), and POA.[1] As evidence evolves in these areas and new observations are reported, there develops a need for updated recommendations. This 2023 update of the Anaphylaxis Practice Parameter addresses what is new or changed since 2015. The JTFPP of the AAAAI and ACAAI also published a GRADE guideline on anaphylaxis in 2020 with highly focused questions and recommendations regarding the risk of biphasic anaphylaxis and the use of antihistamines or corticosteroids to prevent biphasic anaphylaxis, or anaphylaxis due to chemotherapy infusions, aeroallergen rush immunotherapy, and RCM.[2] This 2023 Update is meant to complement the 2020 GRADE guideline, not to replace it.

The foundation for this practice parameter update is the library of knowledge on anaphylaxis that was expertly reviewed in the 2020 GRADE guideline. This included the epidemiology and risk factors, burden of disease for the most common triggers, pathogenesis, treatment strategies and paradigms, and other essential background knowledge on anaphylaxis. In this document, we will update only those areas in which new developments are relevant to the topics under discussion. Our previous anaphylaxis practice parameters remain an important resource for guidance on many clinical areas that are not updated in the current document.[1, 2]

This update focuses on selected topics based on the publication of new and clinically important studies and on the knowledge gaps of concern to members of the AAAAI/ACAAI and to our patients.[6] Despite the advances in these areas, the body of

679 evidence is still limited in relation to most questions and lacking for some. Clinically
680 important questions must often be addressed indirectly through surrogate markers and
681 outcomes, especially when there are low event rates, and the only published studies are
682 observational and do not consistently report the same outcomes or use the same
683 criteria.[2] These realities of anaphylaxis research lead to low or very low certainty of
684 evidence, even when there are moderate to large numbers of patients studied. The goal
685 of this workgroup was to identify the best available evidence of the past 7 years for the
686 specific topics of interest and synthesize an expert assessment of the best clinical
687 practices supported by this evidence.

688 Although the topics in this update are distinct, there are some areas of overlap.
689 Rather than eliminate all duplication, we felt that the reader is better served by having
690 all the relevant information presented when it supports a recommendation. However,
691 the workgroup did make an effort to harmonize the recommendations across all the
692 topics.

Diagnosis of Anaphylaxis

Anaphylaxis is a systemic, usually multi-organ, potentially life-threatening syndrome. The diagnosis is clinical—there are no quintessential symptoms, findings, or laboratory markers. Through the years, the absence of a gold standard for diagnosis has challenged the ability to formulate a consistently accurate, universally accepted, evidence-based definition. Furthermore, the lack of a universal standardized practical definition has contributed to both under-diagnosis and over-diagnosis, the former resulting in inadequate treatment, with possible increased morbidity and mortality, and the latter contributing to anxiety and unnecessary prescription of epinephrine.[7] We will discuss and compare the definitions and criteria for the diagnosis of anaphylaxis and the nomenclature for the clinical patterns of anaphylactic reactions, which are summarized in the list of Key Points in the Diagnosis of Anaphylaxis shown in Text Box 1.

TEXT BOX 1. Key points of consensus in the definition, criteria, and nomenclature of anaphylaxis

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

2. There are similarities and differences between the 2006 NIAID and 2020 WAO anaphylaxis criteria. Further studies should be conducted to validate the 2020 WAO anaphylaxis criteria.

3. Use of the current (2007) Brighton Collaborative Criteria in establishing the diagnosis of anaphylaxis may lead to overdiagnosis of anaphylaxis.

4. Biphasic anaphylaxis is highly likely when the patient develops anaphylaxis after initial signs and symptoms have completely resolved for at least one hour before the onset of repeated anaphylaxis within 48 hours without re-exposure to an allergen trigger.

5. Biphasic anaphylaxis is unlikely in patients without severe anaphylaxis after a 1-hour symptom free observation following resolution of initial anaphylaxis. Biphasic anaphylaxis is more likely to occur with increasing anaphylaxis severity and in patients who have received more than one dose of epinephrine for anaphylaxis treatment.

6. Persistent anaphylaxis is highly likely when anaphylaxis persists for at least 4 hours.

7. Refractory anaphylaxis is highly likely when anaphylaxis continues despite appropriate epinephrine dosing and symptom-directed medical management (eg, intravenous fluid bolus for hypotension). Refractory anaphylaxis increases the risk for anaphylaxis fatality.

8. Anaphylaxis severity is a continuum that results from a combination of risk factors, including those related to the allergen (e.g., allergen dose and route of exposure) as well as the patient (e.g., immune response, behaviors, concomitant medications, and other patient specific factors and comorbidities).

9. Patients with severe anaphylaxis are more likely to demonstrate hypotension and hypoxemia. Severe anaphylaxis is associated with older age, pre-existing cardio-pulmonary disease, and drug etiology.

As evidenced by **Table IV**, the diagnosis of anaphylaxis over the years has varied with the country of origin, group or entity from where it was derived, and the intended application.[8-23] While "multi-organ" has been part of many definitions from 2004 to 2016, a single organ system may exhibit major involvement with more physiologic disruption than others. For example, predominantly cardiovascular or respiratory system involvement may be present in up to 14% and 31% of patients, respectively, with only minor involvement of other systems.[24] Laryngeal, respiratory, and/or cardiovascular involvement are common in fatal anaphylaxis.[25]

Most definitions of anaphylaxis include the word "generalized" and/or "systemic" reaction; however, the ability of patients, caretakers, or bystanders to understand these concepts is uncertain. The WAO (2019 and 2020) anaphylaxis definition is composed of two sentences.[20, 21] The first is similar to the 2006 NIAID definition but with "systemic hypersensitivity" substituted for "allergic" to be more precise (**Table IV**).

Table IV: Anaphylaxis definitions 2001−2021.

Country, region, or organization	Date	Definition	Reference
EAACI	2001	Anaphylaxis is a severe, life-threatening, generalized or systemic hypersensitivity reaction	Johansson et al 2001[8]
ASCIA	2004	Anaphylaxis is a rapidly evolving generalized multi-system allergic reaction characterized by one or more symptoms or signs of respiratory and/or cardiovascular involvement, and involvement of other systems such as the skin and/or gastrointestinal tract.	Braganza et al 2006[9] and Brown et al 2006[10]
USA/NIAID	2006	Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death. [See **Table V** for NIAID anaphylaxis criteria]	Sampson et al 2006[11]

Brighton Collaboration Working Group - International	2007	Anaphylaxis is an acute hypersensitivity reaction with multi-organ-system involvement that can present as, or rapidly progress to, a severe life-threatening reaction. It may occur following exposure to allergens from a variety of sources including food, aeroallergens, insect venom, drugs, and immunizations. Anaphylaxis is set apart from simple allergic reactions (eg, urticaria, allergic rhinitis, asthma) by the simultaneous involvement of several organ systems.	Rüggeberg et al 2007[12]
US PP guidelines	2010	Anaphylaxis is an acute, life-threatening systemic reaction with varied mechanisms, clinical presentations, and severity that results from the sudden systemic release of mediators from mast cells and basophils,	Lieberman et al 2010[13]
WAO	2011	Anaphylaxis is a serious life-threatening generalized or systemic hypersensitivity reaction" and “a serious allergic reaction that is rapid in onset and might cause death	Simons et al 2011[14]
Pakistan	2013	Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death.	Khan et al 2013[15]
EAACI	2014	Anaphylaxis is a severe (potentially) life-threatening generalized or systemic hypersensitivity reaction. This is characterized by being rapid in onset with life-threatening airway, breathing, or circulatory problems and is usually, although not always, associated with skin and mucosal changes	Muraro et al 2014[16]
Germany	2016	Anaphylaxis is a severe, life-threatening, generalized or systemic hypersensitivity reaction. Grade 1: Local with no systemic symptoms. Grade 2:	Niggemann et al 2016[17]

		mild/moderate systemic reaction with skin and/or GI. Grade 3: severe anaphylaxis, systemic with respiratory and/or cardiovascular involvement	
ASCIA	2016	Any acute onset illness with typical skin features (urticarial rash or erythema/flushing, and/or angioedema), PLUS involvement of respiratory and/or cardiovascular and/or persistent severe gastrointestinal symptoms; or any acute onset of hypotension or bronchospasm or upper airway obstruction where anaphylaxis is considered possible, even if typical skin features are not present.	ASCIA Clinical Update[18]
WHO ICD-11	2019	Anaphylaxis is a severe, life-threatening systemic hypersensitivity reaction characterized by being rapid in onset with potentially life-threatening airway, breathing, or circulatory problems and is usually, although not always, associated with skin and mucosal changes.	WHO 2021[19]
WAO	2019 2020	Anaphylaxis is a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death. Severe anaphylaxis is characterized by potentially life-threatening compromise in breathing and/or the circulation, and may occur without typical skin features or circulatory shock being present.	Turner et al 2019[20] and Cardona et al 2020[21]
EAACI	2020	Anaphylaxis is a severe allergic reaction. [Defined in the context of when to use epinephrine autoinjectors]	Kraft et al 2020[22]

ASCIA	2021	Any acute onset illness with typical skin features (urticarial rash or erythema/flushing, and/or angioedema), plus involvement of respiratory and/or cardiovascular and/or persistent severe gastrointestinal symptoms; or any acute onset of hypotension or bronchospasm or upper airway obstruction where anaphylaxis is considered possible, even if typical skin features are not present.	ASCIA 2021[23]
Brighton Collaboration Working Group	2022	Anaphylaxis presents acutely and leads to a marked change in an individual's previous stable condition and is characterized by the following: Rapid progression of symptoms and signs which typically affects multiple body systems (skin/mucosa / respiratory / cardiovascular / gastrointestinal) at the same time or sequentially but occurring over a short period of time (within 1 h of onset of the first symptoms or signs).	Gold et al 2022[26]

AASCIA, Australian Society of Clinical Immunology and Allergy; EAACI, European Academy Allergy and Clinical Immunology; NIAID, National Institute of Allergy and Infectious Disease; PP, practice parameter; WAO, World Allergy Organization; WHO, World Health Organization.

Given the need to facilitate recognition of anaphylaxis for treatment with epinephrine, the NIAID and FAAN convened a multinational and multidisciplinary symposium in 2005 to propose an anaphylaxis definition as well as clinical diagnostic criteria[11] (see **Table V**). These criteria have been widely adopted[27] and were found to be 95% sensitive and 71% specific in a prospective validation study among emergency department (ED) patients.[28] Knowledge deficits regarding anaphylaxis recognition and treatment continue to be demonstrated.[29, 30] In an effort to simplify anaphylaxis diagnostic criteria, in 2019 the WAO Anaphylaxis Committee proposed revisions to the

735 definition for anaphylaxis clinical diagnostic criteria, which was subsequently largely

736 adopted by the WAO 2020 guidance (**Table V**).[20, 21]

737 **Table V: NIAID and WAO side-by-side comparison.[11, 21]**

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 (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia (collapse], syncope, incontinence) 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 (eg, generalized hives, itch-flush, swollen lips-tongue-uvula) b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence) d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)	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 (eg generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING: a. Respiratory compromise (eg dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) b. Reduced BP or associated symptoms of end-organ dysfunction (eg hypotonia [collapse], syncope, incontinence) c. Severe gastrointestinal symptoms (eg severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens 2. Acute onset of hypotension or bronchospasm[a] 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. [a]Excluding lower respiratory symptoms triggered by common inhalant allergens or food allergens perceived to cause “inhalational” reaction in the absence of ingestion.

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 greater than 30% decrease in systolic BP b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline	

738 BP, blood pressure; NIAID, National Institute of Allergy and Infectious Disease; PEF, peak expiratory flow; WAO,
739 World Allergy Organization.
740

741 With regard to the 2020 WAO criteria, although most cases of anaphylaxis are
742 likely to be categorized the same as the 2006 NIAID criteria, there are several notable
743 differences, mostly related to the timing, the associated exposures, or the specific organ
744 systems involved. Some examples are listed here and shown in **Table *VI***.

745 1. While the 2006 NIAID criteria include cases of isolated hypotension following
746 exposure to a known allergen, the 2020 WAO criteria would include reactions
747 with acute onset hypotension, bronchospasm or laryngeal involvement (e.g.,
748 stridor, vocal changes or odynophagia) after exposure to a known or highly
749 probable allergen in the absence of typical skin involvement. Notably, isolated
750 bronchospasm or lower respiratory symptoms triggered by common inhalant
751 allergens would not meet 2020 WAO criteria for anaphylaxis.
752 2. While both the 2006 NIAID and 2020 WAO criteria note that symptom onset
753 would be expected within “minutes to several hours,” the 2019 WAO
754 anaphylaxis committee guidance, which informed the WAO 2020 criteria, also
755 includes a footnote specifically noting that some reactions, such as those

secondary to alpha-gal or immunotherapy, may be delayed up to 10 hours in onset.[20]

3. The 2006 NIAID criteria require “persistent” gastrointestinal involvement to qualify as an anaphylaxis manifestation. In contrast, the 2020 WAO criteria require “severe” gastrointestinal involvement so as to acknowledge that gastrointestinal manifestations can be indicative of anaphylaxis without being persistent.
4. The WAO Anaphylaxis Committee drew attention to the discrepancy internationally between the inclusion of gastrointestinal involvement as a systemic manifestation of food-induced anaphylaxis.[20] Thus, the WAO 2020 anaphylaxis criteria include the phrase, “especially after exposure to non-food allergens” when referring to gastrointestinal organ system involvement as a systemic manifestation of anaphylaxis.[21]
5. Finally, to simplify the definition, the 2020 WAO criteria essentially combines the first and second (of three) 2006 NIAID criteria, creating a definition with only two criteria. Therefore, with the 2020 WAO definition all anaphylaxis cases must have mucocutaneous symptoms except those that meet the second 2020 WAO criterion (**Table V**). For example, cases with dyspnea and persistent vomiting after exposure to a “likely allergen” would meet the 2006 NIAID second criteria but not the 2020 WAO criteria due to the absence of mucocutaneous involvement and absence of manifestations meeting the second 2020 WAO criterion. Furthermore, with the 2020 WAO definition, exposure to a “likely” allergen would not be required for cases with only

mucocutaneous and severe gastrointestinal involvement. For example, cases with acute onset of mucocutaneous and severe gastrointestinal manifestations in the absence of a "likely allergen" would meet the 2020 WAO criteria but not the original 2006 NIAID criteria.

Table VI: Diagnosis of anaphylaxis based on NIAID or WAO criteria for multiple organ system involvement.

Organ System #1	Organ System #2	NIAID Anaphylaxis?	WAO Anaphylaxis?
Skin/Mucosal	Respiratory	Yes	Yes
Skin/Mucosal	CV	Yes	Yes
Skin/Mucosal	GI*	Only if likely allergen exposure)	Yes
Respiratory	CV	Yes	Only if known or highly probable allergen with hypotension[a], bronchospasm[c], or laryngeal involvement[b]
Respiratory	GI*	Only if likely allergen exposure)	Only if known or highly probable allergen with bronchospasm[c] or laryngeal involvement[b]
CV	GI*	Only if likely allergen exposure)	Only if known or highly probable allergen with hypotension[a]
Hypotension[a]	none	Only if known allergen exposure)	Only if highly probable allergen exposure
Laryngeal involvement[b]	none	No	Only if highly probable allergen exposure
Bronchospasm[c]	none	No	Only if highly probable allergen exposure

CV, cardiovascular; GI, gastrointestinal; NIAID, National Institute of Allergy and Infectious Disease; WAO, World Allergy Organization

*GI involvement variably defined as "persistent" (NIAID) or "severe" (WAO).

[a] Hypotension defined as a decrease in systolic BP greater than 30% from that person's baseline, OR i. Infants and children under 10 years: systolic BP less than (70 mmHg + [2 x age in years]) ii. Adults and children over 10 years: systolic BP less than <90 mmHg.

[b] Laryngeal symptoms include: stridor, vocal changes, odynophagia.

[c] Excluding lower respiratory symptoms triggered by common inhalant allergens or food allergens perceived to cause "inhalational" reactions in the absence of ingestion.

Future validation of the 2020 WAO criteria will be helpful in determining their clinical utility. Further multidisciplinary and international consensus on clinical diagnostic criteria will be important to address how clinicians and researchers will: 1) classify isolated acute allergic oropharyngeal or laryngeal angioedema as this would meet the 2020 WAO anaphylaxis diagnostic criteria but not the 2006 NIAID criteria; 2) define what constitutes “severe” gastrointestinal symptoms; 3) determine whether or not gastrointestinal involvement should be recognized as a systemic manifestation of anaphylaxis when accompanied by mucocutaneous involvement secondary to food allergens; and 4) reach consensus with regard to other classification discrepancies noted above.

While both the 2006 NIAID and 2020 WAO criteria were developed for the diagnosis of anaphylaxis with any potential trigger, a case definition for the diagnosis of anaphylaxis occurring as an adverse event following an immunization was proposed by the Brighton Collaboration Anaphylaxis Working Group in 2007.[12] The case definition included sudden onset, rapid progression and multiple organ system involvement (**Table VII**). Diagnostic levels of certainty were based on fulfilling major and minor criteria consisting of signs and symptoms as well as tryptase elevation. A study comparing the 2007 Brighton Criteria with the 2006 NIAID criteria reported a moderate level of agreement between case definitions among a cohort of ED patients; however, a discordant result between definitions was found in 28.1% of cases.[31] The 2007 Brighton criteria differ from the 2006 NIAID and 2020 WAO criteria in notable ways, for example, lip swelling is considered a major criterion for respiratory involvement.[21, 31] Thus, a patient with lip swelling and itchy eyes would meet the case definition of anaphylaxis

819 with Level 2 diagnostic certainty, potentially leading to overdiagnosis of anaphylaxis in
820 the setting of immunizations.[32] Application of the 2006 NIAID or 2020 WAO criteria may
821 be more accurate, but further studies are needed (**Table V**).[33, 34] As a result of
822 increased use during the COVID-19 pandemic, and debate regarding the Brighton
823 Criteria performance in assessing vaccine-associated anaphylaxis compared to NIAID
824 or WAO criteria, the Brighton Collaboration anaphylaxis working group published an
825 updated and revised version 2 of the criteria in late 2022 (**Table VII**). The revised
826 criteria focus the major and minor criteria on the reporting of observable clinical signs,
827 rather than subjective symptoms, and provide a clearer approach to the ascertainment
828 of levels of certainty.[26] These modified 2022 Brighton Criteria may be more consistent
829 with other common case definitions for anaphylaxis.

Table VII: Case definitions and differences between the 2007 (version 1) and 2022 (version 2) Brighton Collaboration anaphylaxis major and minor criteria.[26]

	Brighton Collaboration Criteria Version 1 (2007)	Brighton Collaboration Criteria Version 2 (2022)	Comments
DEFINITION	Anaphylaxis is a clinical syndrome characterized by sudden onset AND rapid progression of signs and symptoms involving multiple (≥2) organ systems, as follows	Anaphylaxis presents acutely and leads to a marked change in an individual's previous stable condition and is characterized by the following: Rapid progression of symptoms and signs which typically affects multiple body systems (skin/mucosa / respiratory / cardiovascular / gastrointestinal) at the same time or sequentially but occurring over a short period of time (within 1 h of onset of the first symptoms or signs).	*Sudden onset* has been removed in BC-V2 and a clearer description of *rapid progression* has been provided and multi-system involvement is defined more clearly. Both V1 and V2 require rapid progression for all levels of diagnostic certainty.
CRITERIA:			
Major Skin	Generalized urticaria (hives) or Generalized erythema; Angioedema, localized or generalized; Generalized pruritus with skin rash	Urticaria (hives)at a location other the vaccine administration site; Angioedema of the skin (swelling) at a location other the vaccine administration site; Generalized (widespread) erythema (redness) of the skin with itch	Removal of *generalized* as a descriptor for urticaria and angioedema. Urticarial and angioedema at injection site are excluded. Urticarial and angioedema at injection site are excluded.
Minor Skin	Generalized pruritus without skin rash; Generalized prickle sensation; Localized injection site urticarial rah; Red and itchy eyes	Generalized (widespread) erythema (redness) of the skin with itch; Red and/or itchy eyes, bilateral and new onset; Generalized (widespread) erythema (redness) of the skin without itch	Removal of *generalized pruritus without skin rash, generalized prickle sensation, localized injection site urticarial*, as minor criteria. Inclusion of new onset for red and/or itchy eyes.
Major Respiratory	Bilateral wheeze (bronchospasm); Stridor; Upper airway swelling (lip, tongue, throat, uvula, or larynx); Respiratory distress—2 or more of the following: Tachypnoea, increased use of accessory respiratory muscles (sternocleidomastoid, intercostal), recession, cyanosis, grunting	Expiratory wheeze documented by healthcare professional which could be with/out stethoscope; Inspiratory stridor documented by healthcare professional which could be with/out stethoscope; Angioedema of the mucosa of the upper airway - swelling of the tongue, pharynx, uvula and/or larynx unequivocally documented by a healthcare professional - this does not include isolated lip swelling; 2 indicators of respiratory distress:	Inclusion of wheeze, stridor, upper airway swelling documented, by a healthcare professional. Removal of lip swelling as a sign of upper airway angioedema. Inclusion of measured hypoxia with oxygen saturations < 90 %.

		Tachypnoea, Cyanosis, measured hypoxia with oxygen saturations <90 %, grunting, chest wall retractions, increased use of accessory respiratory muscles	
Minor Respiratory	Persistent dry cough; Hoarse voice; Difficulty breathing without wheeze or stridor; Sensation of throat closure; Sneezing, rhinorrhea	Cough and/or sneezing and/or runny nose new onset and persistent	The minor symptoms (reported difficulty breathing, sensation of throat closure) and signs (hoarse voice) have been removed. Minor respiratory symptoms (cough and/or sneezing and/or runny nose) have been retained but it has been specified this should be new onset and persistent.
Major Cardiovascular	Measured hypotension; Clinical diagnosis of uncompensated shock, indicated by the combination of at least 3 of the following: Tachycardia, capillary refill time >3 s, reduced central pulse volume, decreased level of consciousness or, loss of consciousness	Measured hypotension. Loss of consciousness, other than the brief, self-resolving loss of consciousness typical of a vasovagal reaction	The clinical features of uncompensated shock (other than hypotension or loss of consciousness) have been removed as major criteria, to simplify the criteria. Loss of consciousness has been inserted as a major criterion of hypotension. To differentiate vasovagal syncope from anaphylaxis, the caveat 'other than the brief, self-resolving loss of consciousness typical of a vasovagal reaction' has been inserted.
Minor Cardiovascular	Reduced peripheral circulation as indicated by the combination of at least 2 of the following: Tachycardia, a capillary refill time of >3 s without hypotension, a decreased level of consciousness	None	All minor cardiovascular criteria have been removed
Major Gastrointestinal	None	New onset vomiting; new onset diarrhea	Diarrhea and vomiting have been included as major criteria

Minor Gastrointestinal	Diarrhea; Abdominal pain; Nausea; Vomiting	None	All minor criteria have been removed
Major Laboratory	None	Elevated mast cell tryptase	Mast cell tryptase has been included as a major criterion and defined as either: > upper normal limit for laboratory doing test; or > (1.2 x baseline tryptase) + 2 ng/L
Minor Laboratory	Elevated mast cell tryptase	None	
LEVEL OF CERTAINTY:			
Level 1	≥1 major dermatological AND ≥ 1 major cardiovascular AND/OR ≥1 major respiratory criterion	MAJOR skin/mucosal AND ≥ 1 MAJOR system involvement including respiratory and/or cardiac and/or gastrointestinal and/or laboratory	
Level 2	≥1 major cardiovascular AND ≥1 major respiratory criterion OR ≥1 major cardiovascular OR respiratory criterion AND ≥1 minor criterion involving ≥1 different system (other than cardiovascular or respiratory systems) OR (≥1 major dermatologic) AND (≥1 minor cardiovascular AND/OR minor respiratory criterion)	≥2 MAJOR system involvement including respiratory and/or cardiac and/or gastrointestinal and/or laboratory – excludes skin/mucosal involvement and must be from different systems	
Level 3	≥1 minor cardiovascular OR respiratory criterion AND ≥1 minor criterion from each of ≥2 different systems/categories	≥ 1 MAJOR system involvement including respiratory, cardiac, gastrointestinal or laboratory AND ≥1 MINOR system involvement from skin/mucosal or respiratory and must be from different systems.	
Level 4	Reported anaphylaxis with insufficient evidence to meet the case definition	Insufficient information provided for review to meet any level of certainty. This may include reports which document anaphylaxis without a description of any signs and/or symptoms.	
Level 5	Not stated	Sufficient information provided for review and determined not to meet case definition at any level of certainty.	

The course of anaphylaxis can be variable across patients and populations, although one study has reported some consistency among recurrent anaphylaxis for individual patients.[35] For most patients, anaphylaxis is not persistent, refractory, or biphasic[36-39]; however, these subtypes of anaphylaxis are not uncommon.[36-47] Biphasic anaphylaxis is more likely to occur with increasing anaphylaxis severity and in patients who have received more than one dose of epinephrine for anaphylaxis treatment.[2] Additional risk factors for biphasic anaphylaxis include a wide pulse pressure (resulting from early arteriolar dilation), unknown anaphylaxis trigger, cutaneous signs and symptoms, and drug trigger in children.[2, 48, 49] Persistent, refractory, and biphasic anaphylaxis may be defined by clinical criteria (**Table VIII**). *Persistent anaphylaxis* is highly likely when anaphylaxis persists for at least 4 hours.[36] *Refractory anaphylaxis* is highly likely when anaphylaxis continues despite appropriate epinephrine dosing and symptom-directed medical management (eg, intravenous fluid bolus for hypotension).[36] Data from the European Anaphylaxis Registry suggests refractory anaphylaxis accounts for less than 0.5% of severe anaphylaxis cases, with an associated drug etiology (particularly in the perioperative / periprocedural setting) most frequently recognized.[50] Refractory anaphylaxis increases the risk for anaphylaxis fatality (26.2% vs 0.35% in a 2019 European registry, $p < 0.0001$).[50, 51] *Biphasic anaphylaxis* is highly likely when the patient develops anaphylaxis after initial signs and symptoms have completely resolved for at least one hour before the onset of repeated anaphylaxis within 48 hours without re-exposure to an allergen trigger.[36] In a meta-analysis that included 2,890 adult patients with anaphylaxis, the median percentage of patients with biphasic anaphylaxis was 6.5% (range, 0.4%–20%).[42] The median duration between resolution of the initial

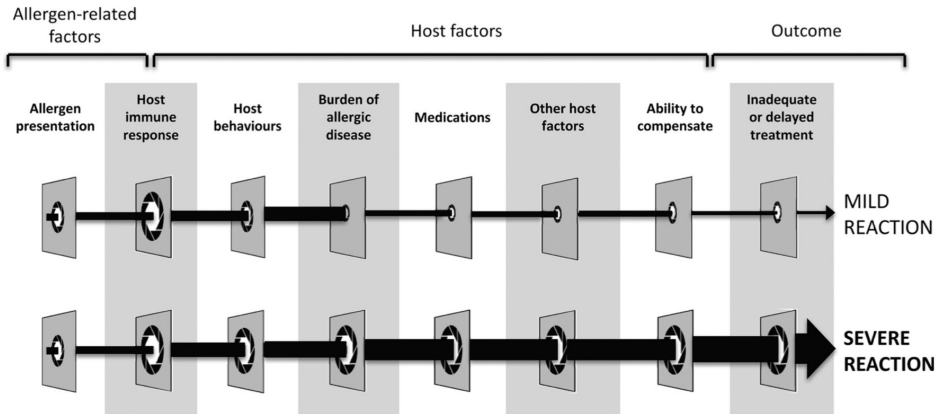
episode and the secondary reaction was 10.5 hours (range, 1.75 hours–17 hours).[42] These findings are in range with other studies of biphasic anaphylaxis.[2, 45, 46, 52] Notably, a 1-hour symptom free observation following resolution of initial anaphylaxis was associated with a 95% negative predictive value (95% confidence interval (CI), 90.9-97.3%) for biphasic anaphylaxis.[42] Persistent anaphylaxis is distinct from biphasic anaphylaxis because in persistent anaphylaxis there is no period of resolution between an initial and a subsequent phase.[36] In one report of 108 episodes of pediatric anaphylaxis requiring hospital admission, anaphylaxis was described as biphasic in 6%, protracted in 1%, and fatal in 2% of patients.[37] Fatal anaphylaxis is a rare outcome.[53, 54] In a population-based epidemiologic study using three national databases, the case fatality rate among patients hospitalized or with ED presentations was between 0.25%–0.33%.[55]

Table VIII: Clinical criteria for diagnosing persistent, refractory, and biphasic anaphylaxis. Adapted from Dribin et al.[36]

Persistent anaphylaxis is highly likely when the following criterion is fulfilled: Presence of symptoms and/or examination findings that fulfill anaphylaxis criteria that persist for at least 4 hours.
Refractory anaphylaxis is highly likely when both of the following 2 criteria are fulfilled: 1. Presence of anaphylaxis following appropriate epinephrine dosing and symptom-directed medical management (eg, intravenous fluid bolus for hypotension). 2. The initial reaction has been treated with 3 or more appropriate doses of epinephrine (or initiation of an intravenous epinephrine infusion).
Biphasic anaphylaxis is highly like when all of the 4 criteria are fulfilled: 1. New or recurrent symptoms and/or examination findings that fulfill anaphylaxis criteria 2. Initial symptoms and examination findings have completely resolved before the onset of new or recurrent symptoms or examination findings. 3. Absence of allergen or trigger re-exposure. 4. New or recurrent symptoms or examination findings occur within 1 to 48 hours from complete resolution of the initial symptoms or examination findings.

Reaction severity is a leading factor in the subsequent course of anaphylaxis, and anaphylaxis severe enough to require hospitalization has been reported to account for up to 22% in some case series.[2, 56-58] It is important to recognize that reaction severity is a continuum that results from a combination of risk factors, including those related to the allergen (eg, allergen dose and route of exposure) as well as the patient (eg, immune response, behaviors, concomitant medications, and other patient specific factors and comorbidities) (**Figure 1**).[59-62] Patients with severe anaphylaxis are more likely to demonstrate hypotension and hypoxemia, and severe anaphylaxis is associated with older age, pre-existing lung disease, and drug etiology.[24] Nevertheless, anaphylaxis is part of a spectrum of acute allergic reactions that range from mild to fatal.[20, 63, 64] Understanding and communicating anaphylaxis severity is important for patients and their families, primary care providers, emergency physicians, hospital physicians, allergy specialists, school personnel, public health authorities, food providers, and researchers.[59] Any definition of anaphylaxis severity must clearly inform all stakeholders.

Figure 1: Risk factors for severe allergic reactions. Reproduced from Dubois et al and Smith et al.[61, 62]



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891 Multiple severity grading systems have been developed,[17, 59, 65-67] and the term
892 "severity" can have different meanings to patients, clinicians, and investigators.[59, 65] In
893 1977, Ring and Messmer proposed a four category classification system to describe
894 severity of reactions to colloid volume substitutes, but this system was not specific to
895 anaphylaxis.[68] The Ring and Messmer classification was subsequently modified such
896 that Grade I represents isolated mucocutaneous involvement, Grade II mild to moderate
897 severity multi-organ system involvement, Grade III life-threatening symptoms in a single
898 organ system or more severe multiple organ system involvement, and Grade IV cardiac
899 or respiratory arrest.[69, 70] Additional grading schemes have been proposed through the
900 years. An approach involving five categories proposed by Sampson for grading of food-
901 induced anaphylaxis was subsequently adopted by the EAACI in 2007.[71, 72] In 2004,
902 Brown[65] proposed a simple classification system for the range of hypersensitivity
903 reactions, with mild reactions limited to cutaneous manifestations; moderate reactions
904 characterized by features suggesting respiratory, cardiovascular, or gastrointestinal
905 involvement; and the most severe grades characterized by hypoxia, hypotension, and/or

neurologic compromise) (**Table IX**). Many clinicians continue to employ the 2010 WAO Subcutaneous Immunotherapy Systemic Allergic Reaction Grading System[73], often applying modifications based on age and allergen trigger.[21, 67, 74] Recently, the 2012 Consortium for Food Allergy Research Grading Scale for Systemic Allergic Reactions, characterized by 5 severity levels, was updated through a collaboration of expert opinion with industry input to consider response to therapy in assignment of severity grade.[75] In addition, the Food Allergy Severity Score was recently developed using the EuroPrevail outpatient clinical cohort of 8,232 food allergy reactions.[76]

Table IX: 2004 Brown grading system for hypersensitivity reactions. Adapted from Brown, 2004.[65]

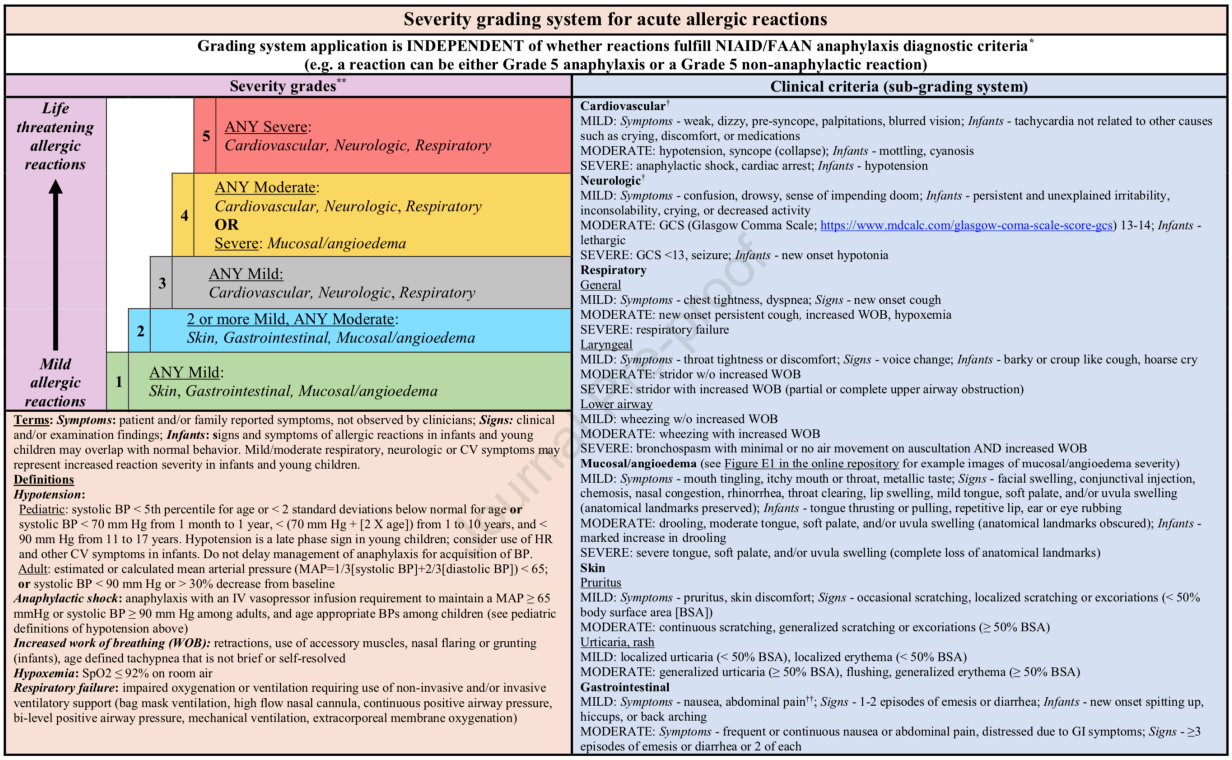
Mild: Signs and symptoms isolated to the skin, such as generalized erythema, urticaria, periorbital edema, or angioedema
Moderate: Signs and symptoms suggesting respiratory, cardiovascular, or gastrointestinal involvement, such as dyspnea, stridor, dizziness (presyncope), diaphoresis, chest or throat tightness, or abdominal pain
Severe: Signs and symptoms reflective of hypoxia, hypotension, and/or neurologic compromise, such as cyanosis or oxygen saturation $\leq$ 92%, hypotension (systolic blood pressure < 90 mm Hg in adults), confusion, collapse, altered level of consciousness, or incontinence.

There are limitations to existing anaphylaxis severity scoring systems. For example, the Brown severity grading system, developed using a statistical analysis of the relationship between individual reaction features and subsequent treatment with epinephrine and patient outcomes, uses observable signs and symptoms without the use of physiologic measurements (e.g., blood pressure and oxygen saturation).[65] Grade 1 would not be considered anaphylaxis while Grade 2 and Grade 3 would fulfill the definition of anaphylaxis and could be adopted as an indication to immediately administer epinephrine in both the community and medical settings.[65] However, such a

grading system may not be ideal in real-time decision-making as affected subjects may change from a less severe to more severe grade quickly; arguing for consideration of epinephrine in milder reactions if risk of progression is a concern. This may be particularly relevant with rapid onset of signs or symptoms following exposure to a suspected allergen. In an analysis of 259 food-induced anaphylaxis episodes from 157 children, a 24.7%–70.2% disagreement was observed across multiple severity score rating systems. The authors of this study highlighted that the presence of anaphylaxis is not requisite for epinephrine use during an allergic reaction, and conversely, use of epinephrine does not necessitate a diagnosis of anaphylaxis be made.[77]

In 2021, a severity grading system for allergic reactions proposed by Dribin et al[63] resulted from an expert consensus and synthesis of the many prior grading scales with additional granularity but also added some degree of complexity (**Figure 2**). An advantage of the 2021 grading system is that it allows grading of allergic reactions from mild to severe with or without requiring a definition of anaphylaxis. This system is clinically intuitive, but also quite nuanced, so will likely require the use of decision support tools or memory aids to be most effective. While derived from expert consensus of a 21-member multidisciplinary panel, the 2021 grading system still requires validation. Using a “Best-Worst Scaling” exercise, Stafford et al[78] evaluated ten severity grading systems, concluding that geographic location of the healthcare provider may impact severity assessment and that all scoring systems have limitations in discriminating anaphylaxis severity.

Figure 2: Anaphylaxis consensus severity grading system. Reproduced from Dribin et al 2021.[63]



Severity grading system for acute allergic reactions

**Grading system application is INDEPENDENT of whether reactions fulfill NIAID/FAAN anaphylaxis diagnostic criteria*
(e.g. a reaction can be either Grade 5 anaphylaxis or a Grade 5 non-anaphylactic reaction)**

Severity grades**		Clinical criteria (sub-grading system)
Life threatening allergic reactions ↑	5 ANY Severe: *Cardiovascular, Neurologic, Respiratory*	**Cardiovascular**† MILD: *Symptoms* - weak, dizzy, pre-syncope, palpitations, blurred vision; *Infants* - tachycardia not related to other causes such as crying, discomfort, or medications MODERATE: hypotension, syncope (collapse); *Infants* - mottling, cyanosis SEVERE: anaphylactic shock, cardiac arrest; *Infants* - hypotension **Neurologic**† MILD: *Symptoms* - confusion, drowsy, sense of impending doom; *Infants* - persistent and unexplained irritability, inconsolability, crying, or decreased activity MODERATE: GCS (Glasgow Comma Scale; https://www.mdcalc.com/glasgow-coma-scale-score-gcs) 13-14; *Infants* - lethargic SEVERE: GCS <13, seizure; *Infants* - new onset hypotonia **Respiratory** General MILD: *Symptoms* - chest tightness, dyspnea; *Signs* - new onset cough MODERATE: new onset persistent cough, increased WOB, hypoxemia SEVERE: respiratory failure Laryngeal MILD: *Symptoms* - throat tightness or discomfort; *Signs* - voice change; *Infants* - barky or croup like cough, hoarse cry MODERATE: stridor w/o increased WOB SEVERE: stridor with increased WOB (partial or complete upper airway obstruction) Lower airway MILD: wheezing w/o increased WOB MODERATE: wheezing with increased WOB SEVERE: bronchospasm with minimal or no air movement on auscultation AND increased WOB **Mucosal/angioedema** (see Figure E1 in the online repository for example images of mucosal/angioedema severity) MILD: *Symptoms* - mouth tingling, itchy mouth or throat, metallic taste; *Signs* - facial swelling, conjunctival injection, chemosis, nasal congestion, rhinorrhea, throat clearing, lip swelling, mild tongue, soft palate, and/or uvula swelling (anatomical landmarks preserved); *Infants* - tongue thrusting or pulling, repetitive lip, ear or eye rubbing MODERATE: drooling, moderate tongue, soft palate, and/or uvula swelling (anatomical landmarks obscured); *Infants* - marked increase in drooling SEVERE: severe tongue, soft palate, and/or uvula swelling (complete loss of anatomical landmarks) **Skin** Pruritus MILD: *Symptoms* - pruritus, skin discomfort; *Signs* - occasional scratching, localized scratching or excoriations (< 50% body surface area [BSA]) MODERATE: continuous scratching, generalized scratching or excoriations (≥ 50% BSA) Urticaria, rash MILD: localized urticaria (< 50% BSA), localized erythema (< 50% BSA) MODERATE: generalized urticaria (≥ 50% BSA), flushing, generalized erythema (≥ 50% BSA) **Gastrointestinal** MILD: *Symptoms* - nausea, abdominal pain††; *Signs* - 1-2 episodes of emesis or diarrhea; *Infants* - new onset spitting up, hiccups, or back arching MODERATE: *Symptoms* - frequent or continuous nausea or abdominal pain, distressed due to GI symptoms; *Signs* - ≥3 episodes of emesis or diarrhea or 2 of each
	4 ANY Moderate: *Cardiovascular, Neurologic, Respiratory* **OR** Severe: *Mucosal/angioedema*	
	3 ANY Mild: *Cardiovascular, Neurologic, Respiratory*	
	2 2 or more Mild, ANY Moderate: *Skin, Gastrointestinal, Mucosal/angioedema*	
Mild allergic reactions ↓	1 ANY Mild: *Skin, Gastrointestinal, Mucosal/angioedema*	

Terms: *Symptoms*: patient and/or family reported symptoms, not observed by clinicians; ***Signs:*** clinical and/or examination findings; ***Infants*: s**igns and symptoms of allergic reactions in infants and young children may overlap with normal behavior. Mild/moderate respiratory, neurologic or CV symptoms may represent increased reaction severity in infants and young children.

Definitions

***Hypotension*:**
Pediatric: systolic BP < 5th percentile for age or < 2 standard deviations below normal for age **or** systolic BP < 70 mm Hg from 1 month to 1 year, < (70 mm Hg + [2 X age]) from 1 to 10 years, and < 90 mm Hg from 11 to 17 years. Hypotension is a late phase sign in young children; consider use of HR and other CV symptoms in infants. Do not delay management of anaphylaxis for acquisition of BP.
Adult: estimated or calculated mean arterial pressure (MAP=1/3[systolic BP]+2/3[diastolic BP]) < 65; **or** systolic BP < 90 mm Hg or > 30% decrease from baseline

***Anaphylactic shock*:** anaphylaxis with an IV vasopressor infusion requirement to maintain a MAP ≥ 65 mmHg or systolic BP ≥ 90 mm Hg among adults, and age appropriate BPs among children (see pediatric definitions of hypotension above)

Increased work of breathing (WOB): retractions, use of accessory muscles, nasal flaring or grunting (infants), age defined tachypnea that is not brief or self-resolved

***Hypoxemia*:** SpO2 ≤ 92% on room air

***Respiratory failure*:** impaired oxygenation or ventilation requiring use of non-invasive and/or invasive ventilatory support (bag mask ventilation, high flow nasal cannula, continuous positive airway pressure, bi-level positive airway pressure, mechanical ventilation, extracorporeal membrane oxygenation)

The severity grading system is designed for use across the spectrum of acute allergic reactions as depicted by the vertical arrow (mild to life threatening reactions), whether they fulfill criteria for anaphylaxis or not.

** For patients with multiple symptoms, reaction severity is based on the most severe symptom; symptoms that constitute more severe grades always supersede symptoms from less severe grades. The grading system can be used to assign reaction severity at any time during the course of reactions; reactions may progress rapidly (within minutes) from one severity grade to another. The grading system does not dictate management decisions; reactions of any severity grade may require treatment with epinephrine.

† Patients with severe cardiovascular and/or neurological involvement may have urinary or stool incontinence. However, the significance of incontinence as an isolated symptom is unclear, and it is therefore not included as a symptom in the sub-grading system.

†† Abdominal pain may also result from uterine cramping.

Question: What is the role of serum tryptase measurements in anaphylaxis diagnosis?

Recommendation 1 (CBS): We recommend obtaining a bST in patients presenting with a history of recurrent, idiopathic, or severe anaphylaxis, particularly those presenting with hypotension.

Strength of Recommendation: Strong

Certainty of Evidence: Moderate

Recommendation 2 (CBS): We suggest drawing an acute phase tryptase level as early as possible during a suspected anaphylactic event (ideally within 2 hours after onset of symptoms). A second (baseline) tryptase measurement should be drawn at a later time for comparison to determine if there was a significant elevation.

Strength of Recommendation: Conditional

Certainty of Evidence: Moderate

Recommendation 3 (CBS): We suggest clinicians consider evaluation for HαT in patients with elevated bST (greater than 8 ng/mL).

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Recommendation 4 (CBS): We suggest clinicians consider evaluation for mastocytosis, including a bone marrow biopsy, for adult patients with severe insect sting anaphylaxis or recurrent IA, particularly those with a predictive REMA score.

Strength of Recommendation: Conditional

Certainty of Evidence: Moderate

The differential diagnosis and diagnostic work-up for patients presenting with suspected or presumed anaphylaxis is broad (**Table X**, **Figure 3**).[1] Diagnostic work-up relies on a thorough clinical history with attention to patient age, sex, medical and atopic history, concurrent mediations, possible triggers, symptom pattern, timing of onset, concomitant factors (eg exercise, viral infection, medications, menstrual status, stress), symptom duration, response to treatment (epinephrine), and number of episodes, with very focused testing to examine for IgE-mediated triggers (e.g., skin and/or serum testing).[1] As part of the diagnostic evaluation, it is imperative to confirm the events in question are indeed anaphylaxis, classically by showing objective signs of mast cell activation on physical examination (eg urticaria, wheezing on lung auscultation, or hypotension) or by elevated tryptase to rule out mimickers of anaphylaxis (**Table X**).[79, 80] One must realize that when evaluating for an elevated acute tryptase, a serum tryptase level above the lab-defined normal value (e.g., > 11.4 ng/ml in many labs) may not detect all episodes of anaphylaxis. Rather, a change in tryptase above a patient's bST may offer a more sensitive assessment of systemic mast cell activation. Expert consensus has suggested an acute serum total tryptase level at least 20% plus 2 ng/ml over the patient's bST level is evidence of systemic mast cell activation.[81, 82] While this equation was proposed to aid in diagnosis of MCAS rather than anaphylaxis, it has been validated in perioperative anaphylaxis in one study, suggesting a specificity of 91% and sensitivity of 78% (in this cohort, the positive and negative predictive values were 98% and 44%, respectively).[79] Questions remain regarding the overall utility of using this equation for anaphylaxis in general (e.g., what is the normal temporal intrapersonal variance in tryptase and what is the value in food-induced anaphylaxis).[80]

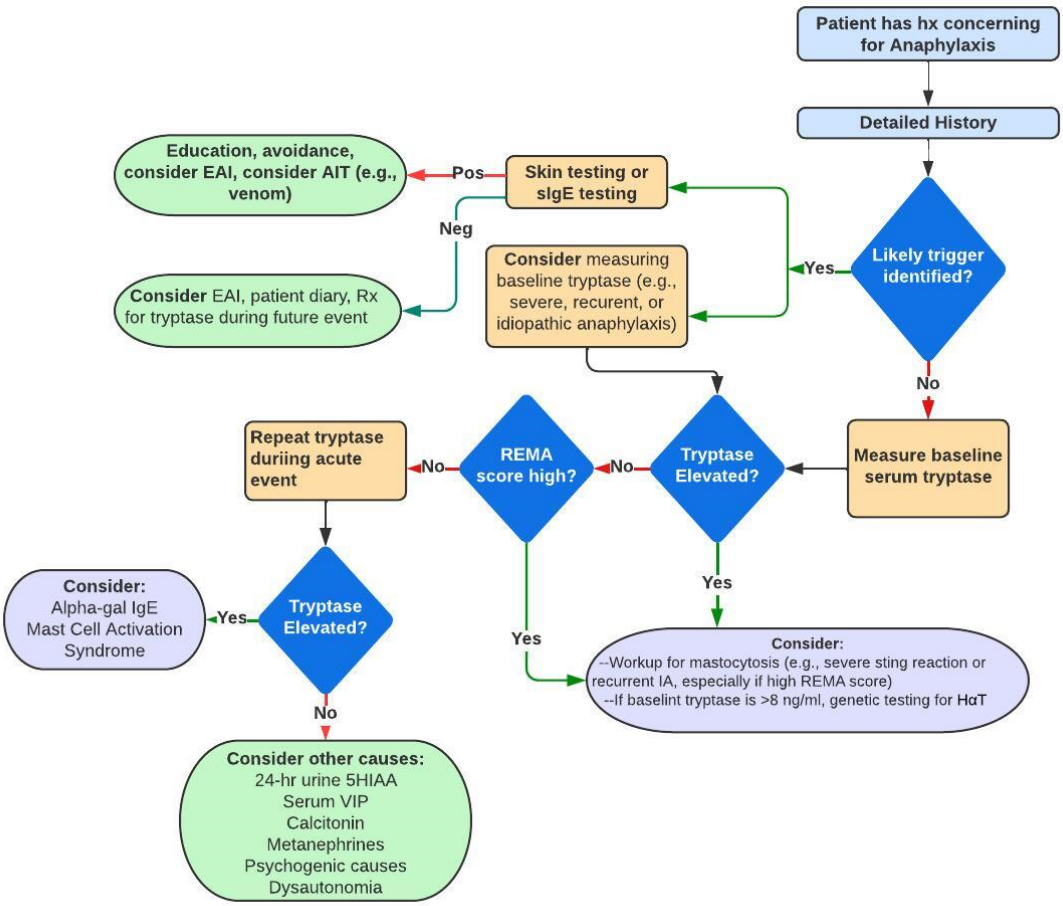
For example, Mateja et al[82] demonstrated that significant variability may occur in bST levels and that among individuals with an elevated tryptase due to an underlying mast cell disorder, one-quarter of individuals exceeded the 20% plus 2 ng/ml threshold on serial asymptomatic measurements; they found that a ratio of acute/baseline tryptase of 1.685 was able to better identify anaphylaxis (sensitivity 94.4%, specificity 94.4%). It has been suggested that even more nuanced cut-off values could be tailored to the index of clinical suspicion,[82] suggesting a cut-off ratio of 1.868 when clinical suspicion of anaphylaxis is low and a ratio of 1.374 when clinical suspicion is high. An online calculator has been published to facilitate use of this particular approach at https://triptase-calculator.niaid.nih.gov.[83] Thus, currently we do not recommend using the 20% plus 2 ng/ml equation alone to diagnose anaphylaxis.

Table X: **Anaphylaxis differential diagnosis. Adapted from Lieberman et al 2015.[1]**

Anaphylaxis • Anaphylaxis due to known allergens – e.g., foods, drugs, insect sting, latex • Anaphylaxis associated with physical stimuli – e.g., exercise, cold, heat • Anaphylaxis associated with both – e.g., food-dependent exercised-induced • Idiopathic
Mastocytosis and Mast Cell Activation Syndromes, Hereditary α-tryptasemia
Vasodepressor reactions • Vasovagal
Flushing Syndromes • Neuroendocrine tumors e.g., carcinoid, pheochromocytoma • Vasoactive intestinal peptide secreting tumor
Restaurant Syndromes • Scombroidosis • Monosodium glutamate

Non-organic Causes: • Anxiety/Panic syndromes (may include pruritus, flushing, urticaria) • Munchausen syndrome (factitious anaphylaxis) or Munchausen by proxy • Vocal cord dysfunction syndrome • Undifferentiated somatoform anaphylaxis • Prevarication anaphylaxis
Miscellaneous • Hereditary angioedema accompanied by rash • Capillary leak syndrome • Red man syndrome • Autonomic dysfunction

Figure 3: Diagnostic evaluation of the patient with a history of anaphylaxis. 5HIAA, 5- hydroxyindolacetic acid; AIT, allergen immunotherapy; EAI, epinephrine autoinjector; HαT, hereditary α-tryptasemia; IA, idiopathic anaphylaxis; REMA, Red Espanola MAstocitosis; VIP, vasoactive intestinal peptide.



Since publication of the 2015 anaphylaxis parameter, there are two updated considerations for evaluating patients with recurrent mast cell-mediated symptoms/recurrent IA. The first is examination not only for elevated bST (as a marker for mast cell disease), but when appropriate, for HαT. HαT is an inherited increase in the α-tryptase-encoding Tryptase α/β-1 (TPSAB1) gene copy number resulting in elevated bST (usually greater than 8 ng/ml).[84, 85] Evidence suggests that TPSAB1 gene copy number encoding α-tryptase significantly influences bST levels, and HαT genotyping could be considered in individuals with tryptase levels above 8 ng/mL.[86, 87] Incorporating copy number can be useful in determining if further evaluation of a clonal mast cell evaluation may be warranted (https://bst-calculater.niaid.nih.gov).[88] HαT occurs in 5-7% of people in unselected populations[89], and while many individuals with HαT are asymptomatic, there are data to suggest that it is often accompanied by a wide range of symptoms.[90] HαT has been reported more frequently in patients with severe symptoms of anaphylaxis in patients with IgE-mediated allergies (such as Hymenoptera venom allergy), with or without mastocytosis, and thus should be considered in evaluation of patients presenting with possible anaphylaxis.[91, 92] Our understanding of HαT is incomplete, and at this point the degree to which the diagnosis alters management is uncertain.[87, 93] Still, HαT should be considered in the differential diagnosis of patients with elevated bST and recurrent or severe anaphylaxis.

Second, there have been scoring systems developed to help determine when patients with recurrent mast cell-mediated symptoms or recurrent IA warrant bone marrow biopsy to look for underlying mastocytosis or a clonal mast cell disorder. The

first of these was published from Spain (referred to as the REMA score) and included many patients with insect venom anaphylaxis (

Figure 4).[94] A more recent study in the US describes the NICAS score in patients with IA (none had venom anaphylaxis;

Figure 4).[95] In this study, 14% of patients with IA were diagnosed with a clonal mast cell disorder. The NICAS score incorporates evaluation of the KIT D816V mutation. Although evidence suggests that in many patients with a clonal mast cell disorder even the most sensitive test for this mutation in the peripheral blood may be negative,[96] within the NICAS score the predictive value may improve. The REMA score has been validated and modified in other studies.[97, 98] The scoring systems are established only in adults, and advise that male sex, lack of angioedema/urticaria, and presence of hypotension/syncope during episodes suggest increased likelihood for clonal disease, and thus consideration for biopsy.[94, 95, 97, 99] However, bone marrow biopsy may be considered in patients with recurrent or severe anaphylaxis episodes outside of these scoring systems.

Figure 4: Scoring systems to evaluate risk of a clonal mast cell disorder in anaphylaxis. ^Reproduced from Lieberman et al and Carter et al.[95, 99] *Adapted from Alvarez-Twose et al.[94]

REMA Score*		
Variable		Score
Gender	Male	+1
	Female	-1
Clinical Symptoms During Attack	Absence of urticaria and angioedema	+1
	Presence of urticaria and/or angioedema	-2
	Presyncope or syncope	+3
Baseline Tryptase	<15 ng/mL	-1
	> 25 ng/mL	+2
Score <2: Low probability of clonal mast cell disorder Score ≥ 2: Predictive of clinal mast cell disorder		

NICAS^		
Variable		Score
Gender	Male	+1
	Female	-1
Clinical Symptoms During Attack	Absence of angioedema	+1
	Presence of flushing	-1
	Presence of urticaria	+1
	Presyncope or syncope	+3
Baseline Tryptase	<11.4 ng/mL	-1
	> 11.4 ng/mL	+1
Allele-specific PCR	Negative	-1
	Positive	+3
Score <2: Low probability of clonal mast cell disorder Score ≥ 2: Predictive of clonal mast cell disorder		

Question: In what settings should the clinician consider evaluation of alpha-gal allergy?

Recommendation 5 (CBS): We suggest that clinicians consider alpha-gal allergy as a possible cause of recurrent IA in a patient with history of possible tick bite; when appropriate, check an alpha-gal IgE, and advise a trial elimination of mammalian meat if alpha-gal IgE sensitization is detected.

Strength of Recommendation: Conditional

Certainty of Evidence: Moderate

There are accumulating data to suggest that alpha-gal allergy can be a common hidden cause of recurrent anaphylaxis previously presumed to be idiopathic depending on geographical location.[100, 101] As with other allergies, alpha-gal asymptomatic sensitization occurs and does not always equate to clinically reactivity. Clinical history, geographical location, exposure to ticks, and outdoor exposure should all be considered when deciding to order and interpret an alpha-gal IgE level. For example, forest workers in the US[102] and Germany[103] have shown sensitization rates (>0.1 kU/L) of 39.1% and 35.0% respectively. However, in those cohorts, 0% and 2%, respectively, had clinical symptoms of delayed anaphylaxis with mammalian meat. In a South African cohort of patients with delayed meat reactions, the alpha-gal IgE assay had good discriminatory properties when compared to 26 healthy controls, with a positive predictive value and negative predictive value of 92% and 83% at a value of >1.0 kU/L in this sample (although these predictive values may not be generalizable in other populations).[104] Thus, when ordering the alpha-gal sIgE, the clinician should use the history to assess the pre-test likelihood of alpha-gal allergy and leverage shared decision-making with the patient regarding a trial elimination of (and subsequent challenge with) mammalian meat if the test is positive.

Question: Is the diagnosis of anaphylaxis required for administration of epinephrine?

Recommendation 6 (CBS): We suggest that meeting diagnostic criteria for anaphylaxis is not required prior to the use of epinephrine.

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

Question: Is administration of, or response to, epinephrine necessary for the diagnosis of anaphylaxis?

Recommendation 7 (CBS): We suggest that neither the clinical decision to administer epinephrine, nor the clinical response to epinephrine, be used as a surrogate marker to establish a diagnosis of anaphylaxis.

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

Anaphylaxis continues to be under-recognized and undertreated with epinephrine, both in the community and in the healthcare setting;[29, 105-115] however, evidence suggests more appropriate use in locations with systems designed for recognition and treatment.[106, 116] While all cases of anaphylaxis represent a systemic hypersensitivity reaction, not all systemic hypersensitivity reactions fulfill diagnostic criteria for anaphylaxis (e.g., generalized urticaria without additional symptoms following any form of AIT).[77] The potential of progression from a non-anaphylactic systemic hypersensitivity reaction to anaphylaxis to life-threatening anaphylaxis further obfuscates this distinction. Thus, definitions incorporate severity (e.g., hypotension or respiratory distress) to distinguish anaphylaxis from non-anaphylactic systemic hypersensitivity reactions at any point in time.[11, 21]

There may be epidemiologic value in the separation of anaphylaxis from non-anaphylactic systemic hypersensitivity reactions. The definition of anaphylaxis is often confused or intertwined with either the criteria for the diagnosis of anaphylaxis or the

severity grading of an allergic or anaphylactic reaction. Diagnostic criteria and severity grading are of greatest benefit when establishing a retrospective diagnosis of anaphylaxis, particularly for use in research and epidemiological studies, and when trying to predict the risk of severe reaction with future episodes of anaphylaxis. Still, severity assessment continues to be an important, often implicit, driver of anaphylaxis management by clinicians. While the NIAID/FAAN criteria are often used in clinical practice, their diagnostic precision is imperfect.[117]

Anaphylaxis represents a high-grade systemic hypersensitivity reaction. For real-time treatment decisions, withholding epinephrine in the setting of systemic hypersensitivity reactions that do not yet fulfill a particular set of diagnostic criteria for anaphylaxis may result in progression of a systemic hypersensitivity reaction.[63, 118] Thus, meeting anaphylaxis diagnostic criteria is not requisite prior to epinephrine use in treating a systemic hypersensitivity reaction.[29] Conversely, neither the clinical decision to administer epinephrine nor the clinical response to epinephrine should be used as a surrogate marker to establish a diagnosis of anaphylaxis.[30] Early epinephrine treatment of a systemic hypersensitivity reaction may be more effective than delayed treatment.[119, 120] Intramuscular epinephrine is a safe medicine with negligible toxicity at doses recommended for anaphylaxis treatment (0.01 mg/kg of a 1:1000 [1 mg/mL] solution to a maximum of 0.5 mg in adults and 0.3 mg in prepubertal children).[2] However, epinephrine use in patients prior to the development of any symptoms is a low-value practice (providing uncertain benefit with potential for harm at substantial cost), and is associated with a quality of life burden.[121-123] Notably, appropriate use of epinephrine during anaphylaxis improves quality of life and self-efficacy.[124] In addition to

epinephrine, other supportive therapies, such as intravenous fluids and supplemental oxygen, may play an important role in the treatment of anaphylaxis, even prior to the development of hypotension.[125] Of note, use of epinephrine does not mandate universal activation of EMS in the patient who experiences prompt, complete, and durable response to treatment when access to advanced medical care is readily available if needed.[126-128] Anaphylaxis preparedness discussions that include shared decision-making may be useful to help patients understand thresholds for further care (see further discussion with **Recommendation 26**).[129, 130]

A recent expert consensus of knowledge gaps in anaphylaxis was published.[6] Further research efforts are expected to continue to inform knowledge gaps in the area of anaphylaxis diagnosis. These are summarized in **Table XI**.

Table XI. Knowledge gaps in the diagnosis of anaphylaxis.

Future validation of the 2020 WAO criteria will be helpful in determining their clinical utility.
Further multidisciplinary and international consensus on clinical diagnostic criteria will be important to address how clinicians and researchers will: 1) classify isolated acute allergic oropharyngeal or laryngeal angioedema as this would meet the 2020 WAO anaphylaxis diagnostic criteria but not the 2006 NIAID criteria; 2) define what constitutes “severe” gastrointestinal symptoms; 3) determine whether or not gastrointestinal involvement should be recognized as a systemic manifestation of anaphylaxis when accompanied by mucocutaneous involvement secondary to food allergens; and 4) reach consensus with regard to other classification discrepancies between the 2006 NIAID and 2020 WAO criteria.
Further validate acute and bST levels informed by TPSAB1 copy number variation.

Better understand the role of third-party payor coverage of TPSAB1 copy number evaluation in influencing and informing evaluation of patients with suspected mast cell disorders.

bST, baseline serum tryptase; NIAID, National Institute of Allergy and Infectious Disease; TPSAB1, Tryptase α/β-1; WAO, World Allergy Organization.

Anaphylaxis in Infants and Toddlers

There is a dearth of quality data regarding the epidemiology of anaphylaxis in infants and toddlers, though this has been a growing area of interest in the past several years. The available data do agree that food is clearly the most common cause of anaphylaxis in this age group, and that is consistent across the globe.[131-135] In addition, the rate of presentation to the ED for anaphylaxis in this age groups appears to be increasing (at least in the US).[131]

Question: How should anaphylaxis be diagnosed in infants and toddlers?

Recommendation 8 (CBS): We suggest clinicians use current NIAID/FAAN or WAO anaphylaxis criteria to assist in the diagnosis of anaphylaxis in infants/toddlers, since there are no criteria specific to this age group.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Defining what age range constitutes infancy is poorly established for the purposes of allergic diseases, including anaphylaxis.[11, 21] A recent expert panel consensus report recommended emphasizing age rather than weight in defining “infant”, and that their recommendations should broadly apply to both infants and toddlers up to age 36 months.[136] This panel also recommended working within the existing NIAID/FAAN criteria for anaphylaxis as there are no criteria specific for infants that have been created by any allergy or emergency medicine society or regulatory authority. However, the panel recognized that as more data are collected regarding these unique

cases, specific age-based criteria for anaphylaxis may become warranted. The panel also identified knowledge gaps in many areas including: recognition of anaphylaxis cases using claims data and issues that may occur with billing/coding inaccuracies, that epinephrine usage rates may not always correlate with anaphylaxis diagnosis, identifying risk factors that specifically predispose infants (vs children of other ages) to anaphylaxis, how best to recognize symptoms of anaphylaxis in non- or minimally-verbal populations, establishing appropriate epinephrine dosing for infants and toddlers, and lack of a standardized evaluation for patients of this age.[136]

Question: Should age of the infant/toddler experiencing anaphylaxis be used as a predictor of reaction severity?

Recommendation 9 (CBS): We suggest clinicians be aware that, in infants and toddlers, patient age is not correlated with reaction severity.

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

Question: Should lack of prior exposure to an allergen be used as a predictor for anaphylaxis risk?

Recommendation 10 (CBS): We suggest clinicians be aware that anaphylaxis is unlikely to be the initial reaction to a food or medication upon first exposure.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Few nationally representative data exist studying anaphylaxis in this age group. However, the Healthcare Cost and Utilization Project (HCUP) Nationwide Emergency Department Sample, a large, national study of temporal trends of presentation to US EDs from 2006-2015, noted that the proportion of visits for anaphylaxis in infants increased from approximately 20–50 per 100,000 visits through this time period, while overall hospitalizations for anaphylaxis presenting to the ED in this age range fell from 19–6%.[137] Private insurance, male sex, and high income were key factors associated with increased odds of being hospitalized after presenting to the ED for anaphylaxis. However, data from the HCUP Nationwide Inpatient Sample show that general admission rates were stable in infants and toddlers during that same time frame.[138] Overall, fatality from anaphylaxis in any age is rare, and exceptionally rare in infants, though few studies have explored this, and there is a risk of omitted cases potentially confounding low estimates.

Data from interventional clinical trials assessing the early introduction of allergenic solid foods in high- and low-risk infants under the age of 12 months has largely noted that anaphylaxis is an uncommon manifestation of initial reactions, and overall, while severe reactions occur, they are far less common than mild to moderate, primarily cutaneous, reactions.[139-145] Data from an Australian population-based, cross-sectional study of 12-month-old infants showed that fewer than 2.5% of all reactions after initial introduction of the food were severe.[146] A national Korean ED registry which showed that 9.7% of children <24 months (n=93 children out of 558 total participants) who presented with anaphylaxis had what was considered by investigators to be a severe reaction.[147] No clinical data or biomarkers provide a rationale for why reaction

severity should differ based on age, though cofactors that augment severity may be more relevant in older individuals. There may be confounding factors in different geographic locations or ethnic populations.

Question: Do infants and toddlers present with different signs and symptoms of anaphylaxis compared with older children and adults?

Recommendation 11 (CBS): We suggest clinicians be aware that parents of infants and toddlers may report age-specific symptoms that are less often reported by older children and adults.

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

Studies suggest that there are age-related symptom presentation patterns for severe allergic reactions.[148-150] Retrospective studies report that infants and young children more often have skin symptoms as compared to older children whereas infants less often have respiratory symptoms.[148, 149] Subjective symptoms are also more often documented for older children, likely because infants are unable to communicate these types of symptoms. A national parent survey conducted by an advocacy group noted that most parents reported skin symptoms and subtle behavioral signs (pulling/scratching/fingers in ear) as a sign of reactions more frequently in children < 12 months as compared with older toddlers.[151] Some studies suggest that gastrointestinal symptoms may be a common presenting feature in infants, but those retrospective studies are limited by the differing definition of ages of infants and young children and reflect self-reported as opposed to clinician-observed symptoms.

Question: Should infants/toddlers be prescribed the 0.1 mg or 0.15 mg EAI?

Recommendation 12: We suggest clinicians prescribe either the 0.1 mg or the 0.15 mg EAI dose for infants/toddlers weighing less than 15 kg.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Epinephrine is the drug of choice for infant anaphylaxis, as it is at any age. However, perhaps the most significant development in infant/toddler anaphylaxis management has been the introduction of a 0.1 mg EAI for infants weighing 7.5-15 kg where formerly only 0.15 mg and 0.3 mg doses were offered.[136] There is older literature suggesting that epinephrine should be dosed at 0.01 mg/kg, but this was derived empirically and represented an expert consensus regarding an appropriate dose.[1] Thus, the actual necessary and sufficient mg/kg dose is unknown, though the 0.01 mg/kg recommendation seems to be at least anecdotally supported by evidence of efficacy.[152] No data suggest that the 0.15 mg dose was either ineffective or unsafe in this population, even when used at lower weights (including <7.5 kg) where the dose may exceed 0.01 mg/kg. Thus, the necessity of the 0.1 mg dose remains unclear, though this dosing option exists (subject to insurance coverage) as a preference-sensitive choice in children under 15 kg.[1] Data have emerged regarding the importance of needle length in smaller infants or toddlers. Studies (based primarily utilizing ultrasound and inference) suggest that longer needles increase the risk of the needle hitting bone. This could impair the delivery of the epinephrine, cause pain and distress, or lead to needle embedment in bone requiring surgical extraction.[153] There are no studies demonstrating

true intraosseous (IO) injections or if this would affect the efficacy of epinephrine if it occurs.[154, 155]

Research into infant/toddler anaphylaxis continues to evolve as multiple knowledge gaps exist regarding its epidemiology, classification, diagnosis, and management. These are noted in **Table XII**, with recommendations to help guide future research.

Table XII: Summary of key knowledge gaps that require additional research related to anaphylaxis in infants and toddlers.

Lack of data on symptom presentation from well-defined infant anaphylaxis cohorts to better determine whether infants need separate clinical criteria to define anaphylaxis as compared to older children, adolescents and adults.
Lack of data to suggest that anaphylaxis in an infant is associated with changes in core body temperature.
Lack of data to determine if needle length of available 0.1 mg and 0.15 mg autoinjectors provides more optimal intramuscular delivery of epinephrine.
Lack of data to determine if potentially higher doses (eg, >0.01 mg/kg) of epinephrine delivered using a 0.15 mg autoinjector in an infant <10 kg leads to adverse effects.
Lack of long-term data on whether early introduction of allergenic foods in infants' diets will lead to increase in severe allergic reactions and healthcare utilization.

Anaphylaxis in Community Settings

Question: What counseling and education should clinicians provide to patients to help them manage the risk of anaphylaxis in community settings?

Recommendation 13 (CBS): We recommend clinicians counsel patients at high-risk of anaphylaxis to always carry self-injectable epinephrine and teach patients proper indications and use.

Strength of Recommendation: Strong

Certainty of Evidence: Very low

Recommendation 14 (CBS): We recommend clinicians educate patients on avoidance of potential exposure to their allergen(s).

Strength of Recommendation: Strong

Certainty of Evidence: Very low

Recommendation 15 (CBS): We recommend clinicians educate patients that the main route of food-induced anaphylaxis is by ingestion and not contact or inhalation.

Strength of Recommendation: Strong

Certainty of Evidence: Moderate

Anaphylaxis is unpredictable and can occur anywhere, with most cases occurring outside the medical setting. While there is abundant data addressing the frequency and

management of anaphylaxis due to different allergen triggers, there are little data regarding the frequency of anaphylaxis in specific community locations or on effective mitigation strategies by location.

Allergen avoidance is a key management strategy for anaphylaxis prevention. Regarding food-induced anaphylaxis, nearly all reported cases are triggered by ingestion of the allergen. Although contact reactions can cause cutaneous symptoms such as hives or redness at the site of contact, the risk of anaphylaxis from isolated skin contact (without oral transfer) is very low.[156] Similarly, the risk of anaphylaxis due to inhalation of food allergen is very low but has been suspected to occur if there is active aerosolization of the allergen (such as steam from boiling milk) in close proximity.[157] Studies support that casual skin contact or inhalation, as could occur in a community setting, is unlikely to trigger anaphylaxis.[158-160]

Determining the frequency of anaphylaxis in different locations outside the home is difficult, due in large part to variations in study design and categorization of locations outside the home, as well as missing information. **Table XIII** presents the calculated percentage range and the average frequency of anaphylaxis in children and/or adults by reported location.[161-209] The younger the population, the higher the percentage of anaphylaxis events occurring in the “home” location.[210] A study in which 89% of 5,149 participants were children reported that although the initial anaphylaxis event occurred most often at home, subsequent anaphylaxis events increasingly shifted to outside the home, in locations such as schools and restaurants.[208] While fatalities have been reported, they are rare.[192] Fatalities reportedly occurred in homes (21–35%), schools

(10–19%), restaurants (19–20%), hospitals (6%) and unknown locations (36–75%). The average and/or median age for all 265 reported fatalities was early twenties.[192]

Table XIII: Frequency of anaphylaxis in different locations.*

Population Studied		Home	School/Work	Restaurant	Other Home
Children	Studies, n	44	46	26	16
	Average	57%	11%	8%	14%
	Range	37–92%	0–28%	0–17%	3–34%
Adults	Studies, n	4	3	3	
	Average	42%	3%	22%	
	Range	27–60%	2–5%	17–33%	
Age not specified#	Studies, n	8	8	7	
	Average	46%	9%	21%	
	Range	16–68%	4–21%	6–51%	

Average = average frequency across the number of studies
Range = range across the number of studies (wide range across the locations)
References for child[161-204]
References for all ages[169, 192, 202, 205-209]
References for adults[200-202]
* In summarizing the location of possible or confirmed anaphylactic events in this table, we have omitted reported reactions that occurred in an "unknown" location. We have combined reactions that occurred in the following locations under the following labels: school, preschool, or work under "school/work"; restaurant, bar, or take-out under "restaurant"; and friend's, relative's, or neighbor's home under "other home". For the categories of "restaurant" and "other home", we only included studies that reported data for these locations or that accounted for 100% of reactions in other categories.
# When studies report the location of anaphylaxis for "all age groups", the authors usually fail to report the location by age category.

Anaphylaxis in child-care centers and schools

The JTFPP endorses the following GRADE recommendations from 2021 guidelines for the management of allergic reactions in child-care centers and schools.[211]

Question: Should child-care centers and schools implement training for personnel in the management of food allergy, rather than not implementing such training?

Recommendation 16 (GRADE): We suggest child-care centers and schools implement staff training for allergy and anaphylaxis management.

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

Question: Should child-care centers and schools prohibit specific foods site-wide (eg, nut-free schools), rather than not implement such restrictions?

Recommendation 17 (GRADE): We suggest that child-care centers and schools not implement site-wide food specific prohibition, because current research does not support consistent benefits. Special circumstances: It might be appropriate to implement allergen-restricted zones (eg, milk-free table) when there are students who lack the capacity to self-manage.

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

Question: Should child-care centers and schools stock undesignated EAIs that can be used to treat any individuals on school grounds who experiences anaphylaxis?

Recommendation 18 (GRADE): We suggest that child-care centers and schools stock undesignated EAIs that can be used to treat any individual on school grounds who experiences anaphylaxis.

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

The authors of these recommendations from the 2021 GRADE guideline for the prevention and management of allergic reactions in child-care centers and schools found that roughly one in 10 allergic reactions and cases of anaphylaxis in children occur in child-care centers or schools.[211] Across studies, the median reported rate of anaphylaxis in child-care centers or schools was 19 per 100,000 students per year (range: 8–118/100,000).[211] The GRADE guideline conditionally recommended that K-12 child-care centers and schools implement an expert-designed allergy training program for personnel in combination with site-wide protocols for managing anaphylaxis and allergy action plans for managing allergic reactions in students at risk of anaphylaxis. Staff training is linked to short-term improvements in allergy-related knowledge, skills, and preparedness among child-care and school personnel.[211] Limited, low-quality evidence suggests that training and action plans may help reduce the rate of allergic reactions and the need for epinephrine use in students.[176, 211-217]

Studies have not consistently found that food bans improve quality of life[218] or lower the risk of allergic reactions among students.[172, 173, 219] Thus the GRADE guideline conditionally recommends that child-care centers and schools not implement site-wide food prohibitions (eg, “nut-free schools”). The guideline also conditionally recommends against classroom-level foods bans and allergen-free tables, except in cases when students lack the capacity to self-manage avoidance and prevention strategies due to very young age or cognitive or physical impairments.[211]

Additional common-sense strategies for risk reduction have not been formally evaluated but include washing hands before and after eating, avoiding sharing foods

and drinks with others, and checking ingredient lists for allergens. Other steps that child-care centers and schools can take include providing adult supervision during meals and snacks, cleaning surfaces where food is prepared or eaten, and taking steps to avoid students' allergens when planning and implementing classroom activities (e.g., parties, crafts, science projects) or field trips.

The 2021 GRADE guidelines also conditionally recommended that child-care centers and schools stock undesignated EAIs that may be used to treat anaphylaxis in any student, staff member, or other individual that experiences anaphylaxis on site.[211] The US School Access to Emergency Epinephrine Act encourages states to implement policies requiring schools to stock undesignated EAIs for use in emergencies. Undesignated EAIs may be used in cases when student-specific EAIs are unavailable, including for treatment of individuals with no known history of allergy (15–31% of reported cases of epinephrine use at child-care centers and schools are for first-time reactions). At this time, not all states have laws that require schools to have stock epinephrine available.[220]

Anaphylaxis in the restaurant setting

Question: What education should clinicians provide to patients with food allergy regarding anaphylaxis in the restaurant setting?

Recommendation 19 (CBS): We suggest clinicians counsel patients that although US regulations require disclosure of major allergens on labels of prepackaged foods, restaurants are not required to declare ingredients or provide allergy warnings for non-prepackaged foods.

Strength of Recommendation: Conditional

Certainty of Evidence: Very low

Recommendation 20 (CBS): We suggest clinicians counsel patients on safe practices for dining outside of the home.

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

Training of restaurant staff is the mitigation strategy that has been most often examined for the ability to reduce anaphylaxis in the restaurant setting. Knowledge gaps related to food allergy and anaphylaxis have been noted in restaurant and other food service staff, and only a minority of staff receive specific training.[221-223] The effectiveness of such training in reducing rates of anaphylaxis or improving responses to reactions has not been studied.

Additional risk reduction strategies have been employed or suggested for the restaurant industry, but data are lacking on whether these practices affect rates of anaphylaxis. The Food Allergen Labeling and Consumer Protection Act of 2004[224] requires disclosure of major allergens on packaged food items, but the law does not require restaurants or food establishments that prepare food to provide ingredient lists or allergy warnings to customers. Some cities and states in the US have enacted laws related to food allergy awareness and/or signage, but these are not universal. A minority of restaurants list allergens or ingredients on their menu or other signage, a practice that appears to be increasingly adopted.[221] Policies and practices may need to be updated for additional allergens such as sesame which was recently added by the FDA to the list of allergens that require special labelling.

Researchers have used data from a national voluntary online registry to characterize food allergic reactions in restaurants.[225] Cafes, fast food establishments, and Asian restaurants were frequently identified as locations for reactions. Peanut, tree nuts, and milk were the most common triggers. Approximately half the reactions (53.9%) occurred despite a diner informing the restaurant staff of the food allergy, 26.6% occurred when food allergens were declared on the menu, and 13.7% occurred even though the menu declared allergens and food allergy was communicated to restaurant staff. Over a quarter of reactions were treated with epinephrine (28% received 1 dose, 6.2% received 2 doses). Reactions have also been reported after allergen exposures due to take-out foods.[226] In an online survey of parents of food-allergic children ordering take-out, the most common allergens triggering reactions were milk, peanut, and wheat, which often appeared as "hidden allergens." Take-out orders from Asian restaurants were most frequently associated with severe allergic reactions. Diners reported taking a variety of precautions, including writing the allergy in an online order, calling the restaurant to discuss the order, and visually inspecting the dish; however, reactions still occurred. The number of precautions taken by take-out diners who experienced reactions were no less than by those who did not have reactions. **Table XIV** presents potential strategies for safe dining to be considered when counseling patients.

Table XIV: Potential strategies and considerations for safe dining to discuss with patients. Management of anaphylaxis risk is a "shared responsibility" in the restaurant setting (i.e., both the allergic diner and food service staff have roles to play in keeping the diner safe). Clear communication is essential. There is a lack

of high-quality data on specific strategies for safe dining, but the concepts in this table provide a framework based on expert opinion.

	Potential strategies for safe dining to discuss with patients	Comments
1.	Attempt to determine the restaurant's food allergy policy, menu options, and possible accommodations	This is an important step to help ensure those with food allergy have the information they need to make safe, informed choices when dining out. This can be done via speaking to the restaurant or checking online resources.
2.	Disclose allergy to a knowledgeable and responsible food service staff member prior to ordering their meal, discuss which specific foods and ingredients they must avoid and receive assurance that the utmost care will be taken to exclude these allergens and avoid cross-contact.	When speaking with a knowledgeable and responsible food service staff member, the patient or family should request information about all the ingredients in the menu selection and how the food is prepared prior to placing an order. If the diner feels that safe options are not available, they should seek alternative dining options.
3.	Ensure that all dining surfaces have been cleaned between diners to remove any food residue. This is generally the responsibility of the restaurant, but some diners may feel more comfortable cleaning table surfaces themselves, e.g., using disposable cleaning wipes.	Cleaning protocols across restaurants may vary. It is not unreasonable to inquire about the cleaning process that the food service staff use between diners.
4.	Carry a written list (e.g., allergy cards) of food allergens and hidden sources of these allergens to support communication with food service staff. When dining in a restaurant where many food service staff speak a different language from the patient (e.g., foreign travel), consider providing a translation of this list.	Allergy cards (e.g., https://equaleats.com/) are used by some diners with food allergy to communicate their allergy to the food service staff. This can be a useful communication tool, especially when travelling or if English is not the first language of the diner or staff. It can help clearly articulate the diner's food allergy and can be shared with the food service staff in both front- and back-of-house to ensure the proper information is shared with those preparing and serving food to the allergic diner.
5.	Inform dining companions of the food allergy and steps to take in the event of an accidental ingestion and allergic reaction.	When eating with others, allergic diners should tell them in advance about their food allergy and what to do in an emergency situation. It's important to share this

		information so dining companions can help in case of an allergic reaction and assist with the epinephrine administration and/or calling emergency services. Patients should let their dining companions know where to locate their EAI (e.g., patient's purse) and provide instructions on how to use it.
6.	Be aware that there is likely higher risk of peanut, tree nut, and/or milk exposure in Asian restaurants, bakeries, and ice cream shops and practice extra vigilance or possible avoidance of those venues. Be aware that there is likely higher risk of seafood exposure at restaurants that predominantly serve seafood and practice extra vigilance or possible avoidance of those venues.	Patients with an allergy to peanuts, tree nuts, milk, or seafood should be cautious at food service establishments that commonly serve their allergens since it may be very difficult to find safe menu options. The potential for cross-contact may be higher in these establishments because these allergens are more prevalent in the kitchen and depending on the level of training or knowledge of the food service staff, there may or may not be protocols in place to minimize cross-contact. Asking the food service staff about their food allergy policy and practices and their ability to provide accurate and complete ingredient disclosure is important and will help diners with food allergy better understand the potential risks of eating at these establishments or determine if another option would be more appropriate.
7.	Avoid buffets due to higher risk of cross-contact.	Buffets are accessed by multiple diners who may not be cautious about avoiding cross-contact between serving utensils, dishes, etc.
8.	Only eat food prepared specifically for the allergic diner when dining out.	Diners with food allergy should consider not sharing or sampling the food of dining companions because food service staff may have paid less attention to cross-contact.
9.	Consider dining during off-peak hours.	Diners with food allergy may consider eating out during "low-traffic" times (as opposed to the lunch rush or a busy brunch hour), when food service staff may have more time to discuss safe menu options and prepare the allergen-free food.
10.	Follow general recommendations regarding anaphylaxis preparedness and management.	When dining out, it is important to always be prepared to treat a reaction should it occur. As such, diners with food allergy should always carry their EAIs with them when dining out.

1455 EAI, epinephrine autoinjector.

Currently, there are no US mandates for restaurants to have medical emergency kits with epinephrine on site. However, 33 states have passed legislation that allows restaurants to keep stock epinephrine on site,[227] and 31 of these bills exempt prescribers from liability. Despite this, physicians continue to have medico-legal concerns about prescribing stock epinephrine, which poses a barrier to restaurants and other community settings that would like to stock epinephrine. In countries such as Canada, where EAIs can be purchased without a prescription, stock epinephrine programs in community settings may be more feasible.[228]

Anaphylaxis inflight

An allergic inflight emergency is estimated to occur once for every 37,750 flights and for ≤ 1 out of 2 million passengers, with emergency landings reported for <4.4% of these episodes. When patients with peanut and/or tree nut allergy have been surveyed, 1.7–10.7% reported having experienced an allergic reaction while on a commercial flight.[229-231] The nature of these reactions and how many of them meet the criteria for anaphylaxis are not clearly reported in published studies. Epinephrine administration for inflight allergic reactions was reported to have occurred in 10–15% of cases across studies,[229-232] although reports of symptoms suggested that epinephrine might have been indicated in more cases.[230, 232] Food allergens are the primary trigger for inflight reactions, with peanut implicated most frequently as the culprit food.[229-232] It is possible there is underreporting of inflight reactions given past data that 29–50% of reactors notified airline personnel of their reaction.[229-231]

Many airline passengers report using risk reduction strategies similar to those used in restaurants, such as notifying flight attendants of their allergy and bringing safe foods for flights.[233] A 2013 study of international study of in-flight reaction found that certain reported risk mitigation strategies were associated with lower odds of reporting an inflight allergic reaction.[231] However, no prospective studies have examined whether implementation of these strategies lowers the risk of anaphylaxis. Although airline pre-notification is often suggested, it can result in unintended consequences because the Air Carrier Access Act of 1986 allows pilots to refuse boarding to a passenger with an identified medical risk deemed significant enough to pose a potential risk of flight diversion or danger to the passenger.[234] Many airline websites provide some information for allergic patients; however, only a minority offer allergen-free meals for pre-order or allow priority boarding.[235]

Anaphylaxis in community recreational settings

Anaphylaxis can occur in recreational community settings such as parks and other outdoor spaces. In these settings, insect sting allergy is a relevant exposure of concern (occupational exposures will not be discussed in this section). In data from the European Anaphylaxis Registry,[236] half of venom anaphylaxis cases occurred in gardens and parks, 25% in public places or at work, and 25% in an unspecified location. Based on patient questionnaires, insect sting anaphylaxis occurs in 0.34–8.9% of the general population,[237, 238] accounts for 1.5–50% of ED visits for anaphylaxis, [53, 237] and is responsible for 13–33% of all fatal cases of anaphylaxis.[53] Measures for minimizing

chances of insect stings have been suggested in the 2016 stinging insect hypersensitivity practice parameters.[239]

There are other causes and settings for anaphylaxis related to community recreational activities both indoors and outdoors, such as food-dependent exercise-induced anaphylaxis and outdoor dining. However, there is no data quantifying the frequency of these events in the community setting. There is also limited information on the location of drug reactions in the community setting. Allergy to beta-lactam antibiotics and non-steroidal anti-inflammatory drugs are most common, and the majority of reactions occurring outside the medical setting are likely to occur in the home.

Question: Should clinicians advise use of medical identification (e.g., jewelry or wallet card) for individuals at risk of anaphylaxis?

Recommendation 21 (CBS): We suggest that advising individuals at risk of anaphylaxis to wear or carry medical identification (e.g., jewelry or wallet card) be considered optional. If worn or carried, the wording on medical alert jewelry or wallet cards should be verified for accuracy by a healthcare professional.

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

Many people at risk of anaphylaxis use medical alert jewelry (or wallet cards) to declare their allergies; however, the information listed varies across products, it is not standardized, and there is no requirement for physician verification of accuracy.[240, 241] It is unknown whether medical alert jewelry or wallet cards reduce the risk of anaphylaxis or results in more rapid treatment.

Stock epinephrine in community settings

Question: Should stock epinephrine in community settings be supported?

Recommendation 22 (CBS): We suggest that keeping stock epinephrine in community settings should be encouraged, if feasible.

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

Studies show that in the US, sports facilities, airports, and amusement areas are the most common places where automated external defibrillators are used.[242, 243] Therefore, some people suggest that these same locations should, ideally, have undesignated EAIs available.[244] All states have passed legislation that permits (but does not require) "entities" which vary by state (e.g., camps, theme parks, sports arenas, restaurants, daycare centers, college campuses) to stock undesignated epinephrine for emergency use.[227, 245] Although permitted, it is rare for community settings to have stock epinephrine available. There is a lack of data on the health effects, feasibility, and cost-effectiveness of stocking epinephrine in community settings outside of schools. Some studies have explored people's willingness to share their epinephrine devices (proximity-based community response) as another novel approach to facilitate rapid responses to anaphylaxis in the community.[246, 247]

Knowledge gaps related to anaphylaxis in community settings are listed in **Table XV**. The key points reviewed in this section are summarized in **Table XVI**.

Table XV: Knowledge gaps for anaphylaxis in the community.

Epidemiology	- Accurate estimates of prevalence rates and causes of anaphylaxis in various community settings - Standardized terminology for different locations (such as other homes, restaurants, and public and recreational settings) to facilitate aggregation of data across studies - Common definition of anaphylaxis across studies
Anaphylaxis prevention	- Effective risk mitigation strategies for different community settings
Anaphylaxis management	- Effective training programs for restaurant, airline and other community workers to respond to anaphylaxis emergencies - Feasible and cost-effective process for stocking EAIs in public locations

1544 EAI, epinephrine autoinjector.

1545 **Table XVI: Key points for the clinician on anaphylaxis in community settings.**

Epidemiology	• **Anaphylaxis can occur anywhere.** • Most cases of anaphylaxis occur at home, followed by school as the second most reported location for children and restaurants for adults.
Child-care centers and schools	• Implementation of training programs for child-care and school staff and provision of emergency plans by families may help reduce rates of allergic events. • There is lack of evidence to support implementation of specific allergen restriction policies as a risk reduction strategy. Many strategies used by families and schools are based on common-sense approaches to minimize risk of allergen exposure. • Clinicians should prescribe EAIs and advise students at risk of anaphylaxis to always have them available at their child-care center or school, some of which may not have stock epinephrine on site.
Restaurants	• Restaurants are a location where accidental allergen ingestion can occur. • Clinicians should encourage education of food service staff to improve their knowledge of allergen-safe practices in food preparation, management of allergic reactions, and disclosure of allergens on menus. • Clinicians should counsel patients to clearly communicate with food service staff to ensure that their food is allergen-safe and to have their EAIs available at all times as stock epinephrine is not available in most public locations.
Airplanes	• Anaphylaxis has been reported to occur in airplanes, most often to foods.

	• Clinicians should counsel patients on standard food allergy management practices. Given that the risk of severe reaction is primarily associated with ingestion of a food allergen rather than skin contact or inhalation, steps to prevent unintentional allergen ingestion should be the main priority (e.g., bring own safe food when traveling, read ingredient labels). • While airplane emergency kits in the US contain epinephrine (both 1:1000 and 1:10,000 w/v), drawing up appropriate doses using a needle and syringe in a cramped air cabin mid-flight is very challenging and could lead to delayed treatment. • Stock epinephrine is not available in airports or during transit between destinations. It is therefore imperative that patients are prepared with their own EAIs at all times. • Patients should notify flight crew of any allergic reaction so that inflight assistance and ground-based medical support, if needed, can be accessed.
Other community settings	• Anaphylaxis to drugs and insects as well as food-dependent exercise-induced anaphylaxis and idiopathic anaphylaxis, can occur outside the home, so patients should be counseled on allergen avoidance and having epinephrine available.

1546 EAI, epinephrine autoinjector.

1547

Epinephrine Autoinjectors: When and What to Prescribe

Epinephrine is universally recommended as the first line treatment for anaphylaxis.[2] However, the rate of EAI prescription for patients at risk of anaphylaxis remains suboptimal.[112, 248] Even when clinicians prescribe EAIs, patients do not always adhere to their treatment plans, with researchers reporting suboptimal rates of EAI prescription refills, carriage, and use.[112, 248, 249] This practice parameter provides evidence-informed guidance for EAI prescription, use, and patient education and counseling.

Question: Should clinicians take a risk-stratified approach to EAI prescription?

Recommendation 23 (CBS): We recommend clinicians routinely prescribe EAIs to patients at higher risk of anaphylaxis. When deciding whether to prescribe EAIs to lower risk patients, we suggest that clinicians engage in a shared decision-making process that considers the patients' risk factors, values, and preferences.

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

Allergic reactions range in severity from mild skin manifestations to life-threatening anaphylaxis. The severity of symptoms can vary from one reaction to another. There are risk factors that significantly increase the relative risk of anaphylaxis, although the absolute risk may remain small. A patient's risk of anaphylaxis depends in part on their specific diagnosis, history of prior reaction(s), and the ease with which they

may avoid causative agents or circumstances, as well as whether they have completed AIT. Some subsets of patients have a higher frequency of anaphylaxis and/or greater severity of anaphylaxis compared with other patients. There are patients who feel a substantial psychosocial burden from EAI prescriptions; for others, EAI prescriptions are linked to improved quality of life.[250, 251] When assessing the risk of anaphylaxis and weighing the potential benefits of EAI prescription, clinicians should consider a patient's diagnosis, history of allergic reaction, chance of allergen exposure, and cofactors.

For patients with food allergy, even small amounts of causative allergen may potentially trigger an allergic reaction—including anaphylaxis in some cases. Due to the potential for cross-contamination of food products and gaps in food allergy knowledge among the general public, reactions to causative foods may occur even when patients have taken steps to avoid the food. Food oral immunotherapy (OIT) is a relatively new and promising therapy for food allergy; however, safety and tolerability concerns continue to limit its use in routine clinical practice. Many reactions to OIT are mild and resolve without intervention or with antihistamine alone. However, virtually all clinical trials report some severe allergic reactions.[252] These are most frequently reported during the dose escalation when treatment is initiated and subsequent buildup dosing; however, home maintenance doses can also be associated with severe reactions, even with doses previously tolerated.[253] In a recent systematic review and meta-analysis, high-certainty evidence showed that although current peanut OIT regimens effectively induce desensitization, they are associated with considerably increased risk of allergic reactions, anaphylaxis (22% with OIT vs 7 % at baseline), and epinephrine use (RR=2.7) compared with avoidance or placebo.[254] For these reasons, most

clinicians still prescribe EAIs even to those who have successfully achieved a desensitization regimen.

People with venom or insect bite/sting allergy can take steps to reduce their risk of exposure. However, they may still be bitten or stung. VIT is considered nearly completely effective in preventing life-threatening reactions to stings, although honeybee VIT and fire ant whole body extract immunotherapy offer less complete protection.[239]

It is typically easier for people with latex, drug, or RCM reactions to avoid causative agents and circumstances. Most reactions to drugs and RCM occur in healthcare settings, where healthcare professionals are equipped to administer epinephrine.[255] However, in up to one in ten cases of drug or RCM-induced anaphylaxis, the patient experiences a biphasic reaction, which is likely to occur outside of the healthcare setting.[256, 257] The JTFPP found that the greatest risk factor for biphasic reaction is an initial presentation that requires multiple epinephrine doses to treat anaphylaxis (OR, 4.82; 95% CI, 2.70-8.58).[2]

Some drugs have garnered special attention regarding the risk of anaphylaxis. These include omalizumab, which the FDA approved in 2003 for moderate to severe persistent allergic asthma, in 2014 for chronic idiopathic urticaria, and in 2020 for nasal polyps. Until 2021, omalizumab was only administered under medical supervision, but it is now approved for home-based treatment. Clinical trials among patients with moderate to severe asthma initially reported a risk of omalizumab-induced anaphylaxis of 0.08%, which increased to 0.2% in post-marketing surveillance.[258] Many of the reactions were reported to occur more than 2 hours following injection or after a number of uneventful

doses. In 2007, this led the AAAAI and ACAAI's Omalizumab Joint Task Force (OJTF) to recommend the prescription of EAIs to patients prescribed omalizumab.[259] In a subsequent 2011 review, the OJTF found that omalizumab-induced anaphylaxis most often occurred within the first three injections and within 2 hours following injection.[260] Another review found that 64% of cases occurred within <1 hour of injection, 69% occurred at the first or second dose, and 43% occurred in patients with a history of prior anaphylaxis unrelated to omalizumab.[261] More recent studies have found low-risk of omalizumab-induced anaphylaxis, including in patients with severe asthma.[262-265] Given the drug's demonstrated long-term safety and efficacy, the FDA approved home injection of omalizumab in 2021 for patients with no known history of anaphylaxis to either omalizumab or other agents from the 4th dose onward if determined appropriated by a clinician. Although the FDA has not mandated EAI prescription for home injection of omalizumab, the package insert does indicate that the patient/caregiver should be able to recognize and treat anaphylaxis.

Other potential causes of anaphylaxis include SCIT and SLIT, which provide effective therapies for the treatment of allergic rhinitis, conjunctivitis, and asthma. Rare cases of severe anaphylaxis due to SCIT with aqueous allergen extracts have been identified, including very rare cases of fatal anaphylaxis.[266-268] Potential risk factors in SCIT-associated fatalities include uncontrolled asthma, prior systemic reactions, administration during peak pollen season, suboptimal treatment of anaphylaxis, and dosing errors, to name a few. While the majority of systemic reactions with SCIT occur within 30 minutes of administration, approximately 15% occur after more than 30 minutes. Nearly all severe systemic reactions and fatal reactions with SCIT begin within

the first 30 minutes after injections.[269] Severe anaphylaxis has also been rarely reported in large phase 3 clinical trials on SLIT, but with no reported fatalities. In clinical trials of SLIT for seasonal and perennial allergic rhinitis, treatment-related adverse events have been reported at equal frequencies for subjects with and without asthma. When administering SCIT or SLIT, clinicians must be aware of the potential risk of severe allergic reactions and know how to manage them. Clinicians may elect to prescribe EAIs to patients on SCIT, particularly those with a history of prior anaphylaxis due to any cause, prior systemic reactions to immunotherapy, active asthma, or other potential high-risk factors. In the US, the FDA mandates EAI prescription for patients on SLIT. However, in other countries, this is not an absolute requirement and is left to the discretion of the individual allergist and patient, unless mandated by local regulators.[270, 271]

We found no validated risk-stratification algorithms in the research literature to guide EAI prescription. Drawing on clinical data and expertise, we present a list of low-risk versus higher-risk histories in **Table XVII**. Higher-risk patients are more likely than low-risk patients to experience anaphylaxis and require treatment with EAIs. The benefits of EAI prescription are also more likely to outweigh the financial and psychosocial burdens (**see Recommendation 28**) for higher-risk patients compared with low-risk patients. Some additional factors that are not included in the table may increase a patient's risk of anaphylaxis (e.g., comorbid asthma) or the potential benefits of having epinephrine available should anaphylaxis occur (e.g., residing, studying, working, or traveling in a location with long emergency response times). When a patient with no prior history of anaphylaxis is admitted to the ED or visits a primary care

provider for anaphylaxis they should be given a prescription for epinephrine and recommendation for allergist assessment. Patients with iatrogenic anaphylaxis (e.g., to RCM or drugs) may have less need for epinephrine prescription, but they may still benefit from allergist assessment to clarify their risk and provide counseling on possible precautions.

Table XVII: Likelihood of requiring treatment with prescribed EAI.

	Lower Likelihood	Higher Likelihood
IgE-mediated food allergy		• History of prior systemic allergic reaction following exposure
Pollen food allergy syndrome	• No history of anaphylaxis to causative food	• History of anaphylaxis to causative food
Venom or insect bite/sting allergy	• History of only large local or cutaneous systemic reaction(s) • History of anaphylaxis, but on maintenance VIT or discontinued VIT after more than 5 years of treatment with no high-risk factors	• History of anaphylaxis, not treated with a complete course of VIT • Current VIT, with history of prior systemic reaction(s) to VIT • Honeybee allergy • Elevated basal tryptase level • Frequent exposure
Latex allergy	• Low likelihood of exposure	• Occupational exposure
Drug allergy	• Low likelihood of exposure	• Occupational exposure
Exercise-induced anaphylaxis	•	• All cases
Physical urticarias	•	• Cold-induced
Aeroallergen immunotherapy	• No history of prior systemic reaction(s) to AIT and no relevant comorbidities (e.g., asthma)	• History of prior systemic reaction(s) to AIT and/or relevant comorbidities (e.g., asthma)

AIT, allergen immunotherapy; EAI, epinephrine autoinjector; VIT, venom immunotherapy.

Question: How many EAIs should clinicians prescribe to each patient?

Recommendation 24 (CBS): We suggest that clinicians consider a patient's risk factors for severe anaphylaxis, their values and preferences, and contextual factors when deciding whether to prescribe only one versus multiple EAIs. We suggest they routinely prescribe more than one EAI when patients have previously required multiple doses of epinephrine to treat an episode of anaphylaxis and/or have a history of biphasic reactions.

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

In some cases of anaphylaxis, symptoms only improve or resolve following multiple doses of epinephrine. Biphasic recurrence of signs and symptoms may also occur and require additional doses of epinephrine to treat. To manage the potential risk of anaphylaxis requiring more than one dose of epinephrine, regulatory agencies including the FDA have recommended that patients at risk of anaphylaxis carry two EAIs at all times.[272] In the US, EAIs are currently only sold in twin-packs, and thus, single doses cannot be prescribed. However, some researchers have recently called into question the magnitude of health benefits and cost-effectiveness of universally prescribing multiple EAIs.[273] Shaker et al[273] used Markov modeling to evaluate and compare the cost-effectiveness of different prescribing strategies for patients with peanut allergy. They evaluated: (1) routinely prescribing two EAIs to all patients with peanut allergy; (2) prescribing two EAIs only to patients with a history of anaphylaxis; and (3) prescribing two EAIs only to patients with a history of anaphylaxis that required

multiple EAI doses to treat. The authors tested the model in multiple economies and at different price points. They concluded that at current EAI prices in the US (lowest estimated retail price of $340 for a twin-pack) and with low reported rates of anaphylaxis requiring multiple doses to treat, universally prescribing two EAIs is not cost-effective and has marginal health benefits compared with a risk-stratified approach.[273] They found that universally prescribing multiple EAIs would only be cost-effective in the US if the cost of a single EAI was less than $80 or the probability of needing a second dose to treat anaphylaxis exceeded 25%.

A risk-stratified approach may help clinicians evaluate a patient's risk of requiring multiple EAI doses and guide shared decision-making around EAI prescription. A recent systematic review and meta-analysis found that 7.7% of anaphylaxis cases (all ages, all causes) were treated with multiple doses of epinephrine, including epinephrine administered in the community and/or healthcare settings.[272] In children, milk-induced reactions are more likely to require multiple doses of epinephrine to treat.[274, 275] Risk factors and cofactors for severe and fatal anaphylaxis are listed in **Table XVIII.**[53, 276-282] Consideration of these factors may help inform shared decision-making around EAI prescription. However, it is important to note that the interaction between these factors is complex and varies across patients and exposures. Significant uncertainties limit one's ability to reliably predict the severity of future reactions. The presence of one or more of the factors in **Table XVIII** does not necessarily indicate an absolute need for multiple EAIs, nor does the absence of these factors preclude the possibility of a severe reaction requiring multiple doses of epinephrine to treat. Efforts to identify biomarkers that reliably predict the severity of future reactions are ongoing. The JTFPP's 2020

practice parameter update on peanut allergy diagnosis recommends against the use of skin prick test results, whole peanut serum-specific IgE, or component-specific peanut sIgE to predict the severity of future reactions.[283]

Table XVIII: Risk factors and cofactors potentially associated with severe or fatal anaphylaxis.

Drug-Induced Anaphylaxis	Food-Induced Anaphylaxis	Venom Bite- or Sting-Induced Anaphylaxis	Non-Trigger–Related Cofactors/Risk Factors
• Age > 60 years • Cardiovascular diseases • Respiratory diseases • Antihypertensive drugs	• Adolescence • Uncontrolled asthma • Alcohol consumption • Peanut- or tree nut-induced reaction • Exercise	• Older age • Male sex • Hereditary α-tryptasemia • Mast cell disorders • Cardiovascular diseases • NSAIDs • Antihypertensive drugs	• Mast cell disorders • Infections • Perimenstrual period • NSAIDs • Alcohol consumption • Psychological burden • Exercise • Unknown cause

NSAIDS, nonsteroidal anti-inflammatory drugs.

The decision of when to prescribe multiple EAIs may be guided not only by patients' risk of severe anaphylaxis but also by their values, preferences, and contextual factors. For example, some children attend schools that require them to store one or more EAIs on site rather than carry EAIs to and from campus each day. Such children may require two or more EAIs to meet school requirements while also ensuring adequate access to epinephrine in other settings. Residing, working, or attending school in a location with long emergency response times is another example of a contextual factor that may warrant the prescription of multiple EAIs.

Question: What is the optimal timing for EAI administration in relation to symptoms?

Recommendation 25 (CBS): We suggest that clinicians counsel patients and caregivers to give epinephrine at the first sign of suspected anaphylaxis. We suggest that, in general, clinicians counsel patients or caregivers to not give epinephrine pre-emptively to an asymptomatic patient.

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

There is a lack of high-quality evidence on the effects of early versus delayed epinephrine administration for anaphylaxis. However, the available evidence suggests that early epinephrine use for anaphylaxis may help improve clinical outcomes. Studies have linked delayed epinephrine use following anaphylaxis to increased risk of biphasic reactions[2] and hospitalization.[198, 284, 285] In fatality case series, most patients who died from anaphylaxis did not receive timely treatment with epinephrine.[120, 205, 206, 286] One case series of fatal anaphylaxis found that the median time interval from onset of symptoms to respiratory or cardiac arrest was 5 minutes in drug-induced anaphylaxis, 15 minutes in stinging insect venom-induced anaphylaxis, and 30 minutes in food-induced anaphylaxis.[205] As single-arm observational studies, fatality case series are considered low-grade evidence and do not allow us to compare the odds of survival with versus without epinephrine.

There is no evidence that preemptive use of epinephrine in asymptomatic patients prevents anaphylaxis. A 2018 analysis used Markov modeling to evaluate the cost-effectiveness of pre-emptive epinephrine use in cases when a patient has a known ingestion to an allergen without symptoms.[121] The absolute protective effect of

preemptive epinephrine use in the absence of symptoms was low and not cost-effective.[121] However, the authors note that advice regarding preemptive epinephrine use may be patient preference-sensitive. For example, although there is a lack of evidence on the benefits of preemptive epinephrine use, it is possible that a more proactive approach might be appropriate for patients with a history of rapidly progressive near-fatal anaphylaxis or underlying mastocytosis. Clinicians should engage patients in shared decision-making that considers individual risk factors, values, and preferences.

Question: When should EMS be activated following EAI use?

Recommendation 26 (CBS): We suggest that clinicians counsel patients that immediate activation of EMS may not be required if the patient experiences prompt, complete, and durable response to treatment with epinephrine, provided that additional epinephrine and medical care are readily available, if needed. We suggest that clinicians counsel patients to always activate EMS following epinephrine use, if anaphylaxis is severe, fails to resolve promptly, fails to resolve completely or nearly completely, or returns or worsens following a first dose of epinephrine.

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

Until recently, professional and patient organizations have generally advised patients and caregivers to immediately seek emergency care or activate EMS (i.e., call 911) when anaphylaxis occurs, even if epinephrine is administered and symptoms

resolve.[287-289] However, there is a lack of evidence demonstrating the benefits of universal EMS activation. In 2019, Shaker et al[126] modeled the health and economic outcomes associated with reflex activation of EMS immediately following epinephrine use, compared with a "watchful waiting" approach, in which patients or caregivers only activate EMS following epinephrine administration if signs and symptoms of anaphylaxis do not immediately resolve completely or nearly completely. Assuming that reflex activation would lower the fatality risk by 10-fold, the authors found that the cost of preventing one death through immediate activation was $1,349,335,651. Reflex activation would only be cost-effective if it reduced the fatality risk by 500-fold *and* if 75% of people who received epinephrine required additional care in the ED—both of which are unlikely. However, the authors also note that patient preferences for EMS activation may vary, particularly among groups at high-risk of severe or biphasic anaphylaxis.

During the "stay at home" phase of the initial wave of the COVID-19 pandemic, concerns about the risk of infectious disease exposure, healthcare resource use, and the need for short-term healthcare service rationing led allergy specialists to review and revise their recommendations around EMS activation.[2, 127] Casale et al[127] implemented many of Shaker et al's[126] findings when developing Food Allergy Research and Education's anaphylaxis management algorithm for the COVID-19 context. For patients with a prior history of anaphylaxis that required treatment with multiple doses of epinephrine, intubation, and/or ventilation, Casale et al[127] recommend that EMS should be immediately activated upon recognition of anaphylaxis. For lower-risk patients, they recommend activating EMS when severe signs and symptoms do not promptly resolve

with epinephrine treatment. In the opinion of many members of this panel, it is sufficient for severe signs and symptoms to resolve even if some residual cutaneous symptoms remain. Casale et al[127] recommend careful monitoring for recurrence, with non-urgent follow-up care if there is prompt and complete resolution of severe symptoms following epinephrine use and if patients have ready access to additional EAIs. Patients with a past history of progressively severe or biphasic reactions may require more careful or prolonged observation, as may those with comorbid conditions that may impact response to anaphylaxis and treatment. The recommendations of Casale et al[127] were proposed as an interim measure related to factors affecting EDs and the population at large during that stage of the COVID-19 pandemic. More recently, Casale et al[130] have re-examined these recommendations for extended application beyond the contingencies of the pandemic (**Table XIX**). When developing an anaphylaxis management plan, clinicians should engage patients in a shared decision-making process that take individual risk factors, values, and preferences into account.

Table XIX. Considerations for and against home management of anaphylaxis. Adapted from Casale et al.[130]

Considerations for home management	**Considerations against home management**
• Patients/caregivers engaged in shared decision process	• Patients/caregivers not comfortable with managing anaphylaxis without activating EMS/ED
• Immediate access to at least 2 EAIs	• No availability of EAIs or only 1 EAI
• Immediate access to person(s) who can provide help if needed	• Being alone, without immediate access to person(s) who can provide help if needed

• Clear understanding of the symptoms warranting the immediate use of EAI, availability of the anaphylaxis treatment plan	• Being unaware of the allergic symptoms that warrant the use of EAI • Lack of technical proficiency with administration of EAI
• Familiarity with the EAI device administration technique	• Hesitance about the IM injection (needle phobia)
• Clear understanding of the benefits of early epinephrine treatment in anaphylaxis	• Concerns about the potential epinephrine side effects
• Good adherence to previous treatment recommendations, eg, use EAI for anaphylaxis in the past and use of controller medications for chronic conditions	• Past history of severe/near-fatal anaphylaxis treated with more than 2 doses of epinephrine, hospitalization, intubation
	• Poor adherence to previous treatment recommendations, eg, not administering EAI for anaphylaxis in the past and not using controller medications for chronic conditions

EAI, epinephrine autoinjector; ED, emergency department; EMS, emergency medical services; IM, intramuscular.

Question: What are the adverse events associated with EAI use? Are certain populations at increased risk of adverse events? How should this inform EAI prescription and patient education?

Recommendation 27 (CBS): Serious adverse reactions to IM epinephrine are very rare and should not pose a barrier to the prescription or early administration of

EAIs when indicated. To manage the risk of adverse events, we recommend that clinicians counsel patients and caregivers on the proper use of EAIs, the common side effects, and the need for immediate evaluation and treatment when signs or symptoms of serious adverse events develop.

Strength of Recommendation: Strong

Certainty of Evidence: Low

Epinephrine is generally safe, and there are no absolute contraindications to its use for anaphylaxis. Compared with intravenous administration, IM epinephrine is associated with reduced risk of dosing errors and adverse events.[290, 291] The side effects associated with EAI use are typically mild and transient, with one registry study reporting tremors, palpitations, and anxiety as the most common.[291] A 2018 computer simulation study found that the serious adverse event rate for EAI administration was only 0.73%.[292]

In rare cases, epinephrine use for allergic reactions can cause cardiac adverse events such as hypertension, arrhythmias, or myocardial infarction.[293] When cardiac adverse events do occur, they are rarely associated with IM administration. One observational cohort study found that among patients treated with epinephrine in an ED, adverse cardiovascular events were reported in 4/316 (1.3%) IM administrations.[290] In a registry-based study in Spain, potentially serious adverse events—including high blood pressure, chest discomfort, and electrocardiogram changes—were reported in 4/256 (1.6%) IM or subcutaneous (SC) administrations.[291] Retrospective cohort studies suggest that the risk of adverse cardiac events following epinephrine use is higher in

older patients (age ≥50 years).[294, 295] This may lead to reluctance to prescribe or administer epinephrine to older adults or people with a history of cardiovascular conditions. However, those same populations have increased risk of severe or fatal anaphylaxis.[293, 296, 297] Thus, the authors of case reports, observational studies, and reviews have generally recommended prompt treatment of anaphylaxis with IM epinephrine, even in people with advanced age or other cardiac risk factors.[294, 298-301] Clinicians should counsel patients with cardiac risk factors to seek immediate evaluation and treatment if chest pain or other signs or symptoms of cardiac adverse events develop following epinephrine use.

Other potential adverse events following EAI administration include lacerations and embedded needles. These injuries may result if a patient or caregiver moves during administration, the device discharges off center due to malfunction, or the needle bends after hitting bone.[153, 302] In a 2020 study using EpiPen® trainer devices, researchers found that administering an EAI with a "swing and jab" motion rather than a "place and press" technique may result in more leg movement and increased risk of laceration. More research is needed to evaluate strategies to reduce the risk of EAI-related laceration and other injuries. However, Brown et al[153] have proposed several strategies which we present in **Table XX**.

Improper handling of EAIs can also lead to accidental injection and needlestick injury, commonly in the thumb or other digit.[303] One registry study found that following unintentional exposures to EAIs, most people report only minor to moderate effects.[303] In rare cases, digital ischemia following accidental injection into the thumb or other digit

has resulted in digital amputation.[304] A 2020 review recommended oral phentolamine as the most effective treatment for reducing epinephrine-induced digital ischemia.[304]

Table XX: Proposed strategies to reduce the risk of EAI-related injury.[153]

1. Restrain the patient and firmly immobilize their leg before administering the EAI
2. Control the action of administration as much as possible, using a place and press motion rather than a swing and jab motion
3. Hold the EAI in place for the shortest period of time recommended by the manufacturer
4. Avoid reinserting the needle if it dislodges before the recommended hold time passes

EAI, epinephrine autoinjector.

Question: What are the burdens of EAI prescription? How should this inform EAI prescription and patient education?

Recommendation 28 (CBS): We suggest that clinicians discuss the potential financial and psychosocial burdens of EAIs with patients while engaging in shared decision-making.

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

Recognizing the financial and psychosocial burdens of treatment is important for providing patient-centered care and addressing potential barriers to treatment adherence. A 2018 survey of parents of children with food allergy in the US found that 97% felt financially burdened by the cost of EAIs.[305] The out-of-pocket costs of EAIs vary, depending not only on the specific brand of EAI but also on the patient's drug coverage, their eligibility for manufacturers' coupons or other subsidies, and the pharmacy from which they purchase the device.[306, 307] The cost of EAIs is substantially

higher in the US than in many other countries. In the US, the average wholesale price of two EpiPens® increased dramatically from $113.27 in 2007 to $730.33 in 2016. In comparison, the average wholesale prices of generic EAIs, epinephrine prefilled syringes, and ampules of epinephrine are substantially lower.[308, 309]

In addition to the financial burden, EAI prescription may also have psychosocial effects. While some studies have found that patients with food allergy and their caregivers may have positive feelings about EAIs, other studies have found that EAI prescription is associated with reduced quality of life.[250, 251] In a 2013 Australian study, health-related quality of life was worse in food-allergic children who were provided an EAI, even after controlling for age, anaphylaxis, number of food allergies, and atopic dermatitis.[310] In contrast, a 2022 French study found no association between the provision of an EAI and worse health-related quality of life,[311] and a 2021 Japanese study found no link between EAI possession and mental health outcomes.[312] Some evidence suggests that patient treatment preferences, history of anaphylaxis, and baseline stress may affect the burden of epinephrine prescription and its effects on quality of life.[122, 313, 314] Ward et al[122] specifically noted an interaction effect; epinephrine use was associated with decreased quality of life in general but increased quality of life in caregivers of patients where the device was reportedly used for presumed anaphylaxis. This suggests that using epinephrine to treat reactions that do not meet the criteria for anaphylaxis imposes a greater treatment burden.[122] A 2020 study in the US found that roughly 22% of children with food allergy, 50% of adolescents, and 36% of parents reported anxiety caused by EAIs.[251]

Question: What autoinjector characteristics should clinicians consider when prescribing EAIs?

Recommendation 29 (CBS): When deciding which EAI to prescribe, we suggest that clinicians consider dosage, needle length, affordability, access, and patient treatment preferences.

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

Multiple brands of EAIs are available in the US, including: Auvi-Q® (Kaleo), EpiPen/EpiPen Jr.® (Mylan), and generic versions of EpiPen/EpiPen Jr.® (Viatris, Teva) and Adrenaclick® (Amneal). The FDA has also approved the Symjepi® epinephrine injection device, a prefilled syringe without autoinjector functionality. Some devices are available in other countries but not currently available in the US (e.g., Anapen®, Emerade™, Jext®). Devices vary in their available doses, manufacturer-indicated weight class, and design, including needle length (see **Table XXI**). They also vary considerably in cost (see **Recommendation *28*28**). When deciding which device to prescribe, clinicians may consider these characteristics in relation to patient factors such as age, weight, sex, and insurance coverage. Some patients may also prefer one device over another.

Table XXI: Specifications for EAIs and prefilled epinephrine injection devices.

Name	Dosage	Weight class specified by manufacturer*	Weight class supported by practice	Needle Length**	Pressure

			parameter*		
Adrenaclick®	0.15 mg	15–30 kg	<25 kg	1.17 cm	High
	0.3 mg	≥30 kg	≥25 kg	1.17 cm	High
Anapen®***	0.15 mg	15–30 kg	<25 kg	1.0–1.5 cm	High
	0.3 mg	≥30 kg	≥25 kg	1.0–1.5 cm	High
Auvi-Q®	0.1 mg	7.5–15 kg	<13 kg	0.64–0.89 cm	High
	0.15 mg	15–30 kg	<25 kg	1.14–1.4 cm	High
	0.3 mg	≥30 kg	≥25 kg	1.47–1.73 cm	High
Emerade™***	0.15 mg	15–30 kg	<25 kg	1.5–1.67 cm	Low
	0.3 mg	≥30 kg	≥25 kg	2.21–2.36 cm	Low
	0.5 mg	>60 kg	≥45 kg	2.21–2.36 cm	Low
Epipen Jr.®	0.15 mg	15–30 kg	≤25 kg	1.0–1.5 cm	High
Epipen®	0.3 mg	≥30 kg	≥25 kg	1.3–1.8 cm	High
Jext®***	0.15 mg	15–30 kg	≤25 kg	1.3 cm	High
	0.3 mg	≥30 kg	≥25 kg	1.5 cm	High
Symjepi®	0.15 mg	15-30 kg	≤25 kg	not published	N/A
	0.3 mg	≥30 kg	≥25 kg	not published	N/A

EAI, epinephrine autoinjector.
*The manufacturer-indicated weight classes for EAIs differ from recent recommendations from multiple professional organizations, which are described and endorsed in this practice parameter.
**Needle length may be an important consideration in young infants with low body mass, in women, and in adults with high body mass index (>25). Due to the manufacturing process, there is some variability in the length of EAI needles. The ranges reported in this table represent the lower and upper limits of needle lengths.[315]
***These devices are not currently available in the US.

Dosage

The current standard practice is to treat anaphylaxis with a dosage of epinephrine of 0.01 mg/kg, up to a maximum of 0.3 mg for children and teenagers and 0.5 mg for adults. However, there is a lack of robust data to substantiate this recommendation, and more research is needed to determine the optimal dosing. EAIs are only available in a limited number of premeasured doses for manufacturer-specified weight classes (see **Table XXI**). In the US, the FDA has approved 0.3 mg EAIs for patients weighing ≥30 kg, 0.15 mg EAIs for patients weighing 15–30 kg, and a 0.1 mg EAI (Auvi-Q) for patients weighing 7.5–15 kg.[316] Clinical experience suggests that infants tend to tolerate doses of epinephrine higher than 0.01 mg/kg well, and the JTFPP's 2020 anaphylaxis practice parameter update supports the use of 0.15 mg EAI for infants or children weighing <15 kg.[2] A 0.5 mg EAI (Emerade) is also available in some countries for patients weighing >60 kg.

Using dosages specified by manufacturers, patients will receive increasingly less than the recommended dose as their weight increases.[317] To limit underdosing, the AAAAI, AAP, CSACI, and EAACI support switching to 0.3 mg at 25 kg.[1, 16, 270, 318] The CSACI advises that clinicians may consider prescribing a 0.5 mg EAI (not currently available in USA) for people weighing ≥45 kg.[270] Among teenagers, a small randomized trial of EAI administration found no significant adverse events following IM self-injection with 0.3 mg or 0.5 mg of epinephrine.[319] The 0.5 mg dose resulted in higher plasma catecholamine level than the 0.3 mg dose.

Needle length and pressure

When administering epinephrine for anaphylaxis, the standard recommended

route is IM injection into the mid-outer thigh.[317] The mean needle length and pressure required to trigger an EAI vary from one brand to another (see **Table XXI**).[320] The needle should ideally be long enough to penetrate the deep fascia of the thigh but not so long that it strikes bone or causes IO injection.

Based on ultrasound imaging measurements of skin-to-bone and skin-to-muscle distance, Dreborg et al[155, 321] predicted that low-pressure EAIs (Emerade) posed no risk of IO injection and low-risk of SC injection. For high-pressure EAIs (Auvi-Q®, EpiPen®, Jext®), they found the risk varied by demographic and device. They predicted that in children weighing <15 kg, the risk of IO injection was lower with Auvi-Q® 0.1 mg, compared with EpiPen® Jr. and Jext® 0.15 mg; however, Auvi-Q® 0.1 mg posed higher predicted risk of SC injection than other devices.[155, 321] In a follow-up study, they found that injecting EAIs through thick winter clothing increased the risk of SC injection for all brands—and up to 100% for Auvi-Q® 0.1 mg specifically.[315] Counseling patients to remove heavy clothing before administering EAIs may help mitigate the risk.

Dreborg et al[155] predicted that the risk of IO injection was low in children weighing 15–30 kg and negligible in adults. Ultrasound imaging measurements suggest that among adults, the risk of SC injection is highest in obese women.[321, 322] Both BMI and sex differences in subcutaneous tissue depth may affect the risk of SC injection because women tend to have more subcutaneous fat on their thighs than men.[322] However, Duvauchelle et al[323] found that IM injection does not appear to be an absolute requirement for EAI efficacy. Overweight women were more likely to experience SC injection (n=10/12) compared with non-overweight men (n=1/18).[84] However, when the researchers evaluated the bioavailability of epinephrine following injection, the initial

plasma peak was similar in both groups, and the overall bioavailability of epinephrine was higher in the overweight women.[323] There is emerging evidence that the pharmacokinetics of epinephrine may vary between individual patients and between different devices and methods used for administration.[324, 325]

Accessibility

Manufacturer shortages, patient drug coverage, and other factors may affect the accessibility of EAIs and influence providers' prescribing decisions.[309, 326] Clinicians may ask to review insured patients' drug formularies to learn which EAIs are covered by their insurance. Some uninsured or underinsured patients may be eligible for manufacturer-sponsored coupons or financial assistance programs to help offset the cost of EAIs; however, these programs typically exclude Medicare and Medicaid recipients. Clinicians may also consider prescribing generic EAIs as a more affordable alternative to brand-name EAIs or prescribing prefilled epinephrine syringes or epinephrine ampules with empty syringes as an affordable alternative to EAIs. The Canadian Agency for Drugs and Technologies in Health recently reviewed the available research on the clinical and cost-effectiveness of EAIs versus manual epinephrine administration with an ampule/vial and syringe and found no relevant studies.[327]

Usability and patient preference

Some people may find certain EAIs easier to use, more convenient, or otherwise more appealing than others. When researchers asked adults to simulate EAI administration with trainer devices, they demonstrated lower rates of error with Auvi-Q®

than with EpiPen Jr.® or Anapen®.[328, 329] A 2013 study in the US also found that children and caregivers expressed a preference for Auvi-Q® over EpiPen®.[330] Unlike other EAIs, Auvi-Q® provides audio prompts to guide administration. However, some patients or caregivers may prefer other brands of EAI due to familiarity or other reasons. A 2022 study in Ireland found that caregivers tended to prefer EpiPen® over Anapen®, Emerade®, and Jext®.[331]

Question: What counseling, education, and/or training on epinephrine should clinicians provide to patients and caregivers?

Recommendation 30 (CBS): During visits with patients who have been prescribed EAIs, we recommend that clinicians routinely review the essentials of EAI carriage, storage, and use; encourage patients to regularly practice EAI administration with a trainer device; and discuss strategies to manage barriers to adherence that patients may have experienced.

Strength of Recommendation: Strong

Certainty of Evidence: Low

Many patients and caregivers do not administer epinephrine when indicated, due to a variety of factors.[248, 332] These include suboptimal prescription and carriage of EAIs, gaps in knowledge and lack of comfort in recognizing anaphylaxis and administering EAIs, and fear that administering an EAI may cause harm. Multiple studies demonstrate the benefits of clinician-provided education and counseling for improving EAI-related knowledge, skills, and comfort.[333] However, a single instructional session is not sufficient for sustained improvement.[334, 335] More research is needed to identify the

optimal frequency of EAI education for patients and caregivers, but one study in Turkey suggests that 6-month intervals may be appropriate.[336]

Possessing an EAI trainer device and practicing its use on another person have also been linked to increased rates of proper administration.[337, 338] Hands-on experience with administering active EAIs is beneficial, too. When patients or caregivers administered an EAI for an allergic reaction during a medically supervised oral food challenge, they reported improved EAI confidence, knowledge, and skill that were sustained a year later.[339, 340] Similarly, self-injection with an empty syringe during a supervised clinic visit has been linked to improved comfort with injection among at-risk adolescents.[341] Seeing clinicians administer epinephrine for anaphylaxis during healthcare encounters may also reinforce the importance of epinephrine administration for patients and caregivers.[342]

Patients and caregivers may also benefit from reminders to replace EAIs after the devices have been used or expired. If they forget to replace an expired EAI—or are unable to do so due to manufacturer shortages or other barriers—it is preferable to use the expired device rather than no device at all to treat anaphylaxis. Recent studies have found that expired EAIs retain substantial epinephrine activity (80–90%), well beyond their expiration dates.[343-345] Pediatric doses may degrade more quickly following expiration compared with adult doses.[345]

Despite the demonstrated benefits of EAI education for patients and caregivers, provision of this support remains suboptimal.[346, 347] Clinician-reported barriers to providing EAI education and counseling include lack of time, lack of training devices, lack of role clarity around who is responsible for educating patients, and gaps in

clinician knowledge, including confusion about the different brands of EAIs.[347-349] Proposed strategies to address these barriers include automated implementation of EAI teaching and comfort assessments during check-in at allergy clinics,[346, 350] provision of a dedicated pharmacist who can provide counseling on medication,[347] and provision of EAI training for clinicians.[351-355] Studies have found that in-person training sessions,[355] video education sessions,[351, 352] e-learning sessions,[353, 356] and mixed-method training approaches[354] can help improve EAI knowledge, skills, and confidence among clinicians and students. Some evidence suggests that training clinicians on strategies to identify and address psychosocial barriers to EAI adherence may also yield benefits.[348]

Knowledge gaps regarding prescription and use of epinephrine for anaphylaxis are listed in **Table XXII**.

Table XXII: Summary of key knowledge gaps regarding prescription and use of epinephrine that require additional research.

• Lack of consistent definition of anaphylaxis and clinical criteria for diagnosis across scientific societies and professional organizations
• Lack of validated biomarkers that reliably predict the severity of future allergic reactions
• Lack of validated risk-stratification algorithms for guiding EAI prescription
• Lack of validated strategies to reduce the risk of EAI-related lacerations and other injuries
• Lack of high-quality evidence regarding the…
○ effects of early versus delayed epinephrine administration for anaphylaxis
○ outcomes following reflex EMS activation versus watchful waiting following epinephrine administration for anaphylaxis
○ optimal epinephrine dosing

○ implications of EAI needle length
○ ideal frequency of EAI training for patients and caregivers

2059 EAI, epinephrine autoinjector; EMS, emergency medical services.

2060

Beta Blocker and Angiotensin-Converting Enzyme Inhibitor Medications

Beta blocker medications are widely used for a variety of cardiovascular conditions including hypertension, arrhythmias and congestive heart failure, as well as for prevention of migraine and treatment of glaucoma. These medications have physiologic effects that might affect the severity of anaphylaxis and the response to treatment. Beta blockers may reduce compensatory cardiovascular responses to anaphylaxis, may enhance the release of mast cell mediators, and may interfere with beneficial effects of endogenous and therapeutic epinephrine. Angiotensin-converting enzyme inhibitors have similar uses to BB for patients with cardiovascular conditions, especially in diabetic patients. By interfering with the body's natural renin-angiotensin-aldosterone system, ACEIs block the conversion of angiotensin I to angiotensin II, thereby preventing the breakdown of bradykinin, promoting vasodilation, and may have direct effects on mast cells. In both human and mouse models, BB and ACEI have been shown to increase the severity of anaphylaxis and may have an additive effect when used in combination (which has become a common therapeutic approach in severe cardiovascular disease).[357] Angiotensin receptor blockers (ARBs) may blunt the cardiovascular adaptive compensatory response to shock but do not directly affect the kinin system. There is not sufficient evidence to address whether ARBs differ from ACEIs with respect to the risk of severe anaphylaxis (see specific medications, below). Therefore, ARBs are not addressed in this practice parameter and anything said about ACEI should not necessarily be construed to apply to ARBs.

While there is a widely held assumption that the use of BB and ACEI are contraindicated in all patients who are at risk for potential anaphylactic reactions of any kind, there is conflicting evidence in the literature of the actual risk of these medications.[296, 358, 359] This has become a dilemma for an increasing proportion of patients in a variety of clinical settings including AIT (both SCIT and SLIT), VIT, allergen skin testing, food anaphylaxis, RCM administration, drug infusion/ intravenous immunoglobulin (IVIG), MCAS, IA, and desensitization procedures. The perception of risk is based on data from older studies where most of the BB in use were non-selective (e.g., propranolol, nadolol), with many of the reports not taking into account the confounder of cardiac comorbidities which could independently account for the increased risk of severe anaphylaxis.[296] There is also clinically significant medical risk in stopping or changing the prescribed medications such that the risk of discontinuing the medication may far exceed the risk of more severe anaphylaxis. Given the current propensity to use more cardio-selective beta-blocking agents, and the risk/benefit ratio for each of the interventions, we recommend a shared decision-making discussion between patient, prescribers, and providers to convey the absolute and relative risk of the treatment/procedure while receiving the BB/ACEI, the risk of stopping the BB/ACEI, and alternative medications or procedures. Recommendation to the individual patient should include evaluation of many potential risk factors including the frequency of exposure (to the anaphylaxis trigger), predictability of exposure (expected vs unexpected), severity of underlying cardiovascular condition, additive risk of BB plus ACEI, medical necessity, and benefit of the treatment/procedure.

Framework for risk assessment

It is important to place the clinical questions described here in appropriate context of both potential risks and benefits of these medications in patients who are at risk for future anaphylaxis. A sample framework for this evaluation is shown in **Table XXIII**. The clinician, the patient, and the prescriber (e.g., cardiologist) must consider the benefit of the medication for its prescribed indication, the benefit of the medical procedure or treatment that is said to be contraindicated, the risk of stopping the prescribed medication, the risk of not having the medical procedure or treatment, and the risk of having the medical procedure or treatment while continuing the prescribed medication.

Table XXIII: Framework for evaluation of the benefit and risk of BB or ACEI medication in the patient at risk for anaphylaxis.

Clinical question	Potential Benefits of Treatment	Potential Risks of No Treatment
What is the indication for the medication? Post-MI CHF Tachyarrhythmia Migraine Glaucoma Diabetes	All of these disease states have been shown to derive benefit from BB.	Risks include poorly control heart rate, inadequate secondary prevention of cardiac disease and ongoing symptoms of CHF. Glaucoma often cannot be managed without ocular BB but risk of systemic complications of beta-blockade extremely low. Minimal risk of avoiding BB for migraine prophylaxis as many alternatives now exist.
What is the indication for the intervention? Skin test Initial AIT Mc AIT Initial VIT	Benefit of skin testing includes accurate diagnosis. Benefit of environmental AIT is mainly improved QOL.	Risk of avoiding skin tests includes delayed/inaccurate diagnosis. Risk of avoiding AIT includes ongoing QOL

Mc VIT	Benefit of VIT is reduction of morbidity and elimination of mortality.	burden if pharmacotherapy has failed. Risks of avoiding VIT means ongoing risk of potentially life-threatening anaphylaxis.

AIT, allergen immunotherapy; CHF, congestive heart failure; EAI, epinephrine autoinjector; Mc, maintenance; MI, myocardial infarction; QOL, quality of life; VIT, venom immunotherapy.

In most cases, the risk of stopping the BB or ACEI is greater than the risk of more severe anaphylaxis if the medication is continued. This is partially due to the low inherent risk of anaphylaxis with most medical procedures and treatments and the relatively small incremental risk associated with the medications. Thus, the clinical decision-making often rests on the patient's desire or need for the procedure/treatment and their willingness to accept the potential risk of the medications.

However, the risk of anaphylaxis may be higher for some patients than others. The frequency of natural exposure to potential triggers of anaphylaxis may be very low in some people (e.g., insect sting), but exposure occurs in all patients with food OIT and with food/drug challenges. The exposure is known with AIT/VIT but the risk of anaphylaxis is very low with these. The risk of foregoing certain procedures or treatments, such as AIT in many cases, may be relatively low; however, the risk of foregoing other procedures or treatments, such as VIT for life-threatening sting anaphylaxis, may be significantly higher.

Specific medications

In this document we will generally refer to BB and ACEI together. Although their mechanisms of action differ and the rationale for their potential impact on outcomes of

anaphylaxis differs, there has been little to differentiate their risks from each other in the published reports.

While it is believed that there is less potential risk with beta-1-selective blockers than with non-selective BB, there are insufficient data in the published reports to address this question. Still, when possible, consideration should be given to managing patients at risk for anaphylaxis with a cardio-selective BB so as to minimize the risk, given the more targeted nature of these BB, thus avoiding blockade of the beta-2 adrenergic effects on the airways. Of note, this is a theoretical consideration which lacks high certainty supporting evidence.

There are also scant data on the relative risk of ACEI and ARBs. In one study of angioedema (n=4,511 events) the adjusted odds ratio compared with BB's was 3.04 for ACEI, 2.85 for the direct renin inhibitor aliskiren, and 1.16 for ARBs.[360] In a study of cardiac catheterization, 70 episodes of anaphylaxis occurred during 71,782 exposures. There was no significant difference in the frequency of anaphylactic reactions between controls, BB (mostly beta-1 selective), ACEI or ARB medications.[361] In a study of systemic reactions to immunotherapy injections, there was no difference in the frequency of reaction between ACEI and ARB treated patients.[362] It should not be assumed that ARBs carry the same potential risks as ACEI, but there is not sufficient evidence to recommend either avoidance or safety of ARBs in patients at risk for anaphylaxis.

Stinging insect allergy and venom immunotherapy

Question: Should BB or ACEI be discontinued or changed in patients with a history of insect sting anaphylaxis who are not yet on VIT?

Recommendation 31 (CBS): We suggest that patients with a history of insect sting anaphylaxis who are not on VIT should continue BB or ACEI when the medical necessity of the daily medication outweighs the chance of increased severity of anaphylaxis to a sting.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Question: Should VIT be recommended to patients with a history of insect sting anaphylaxis who are treated with BB or ACEI?

Recommendation 32 (CBS): We suggest that VIT should be recommended to patients with a history of insect sting anaphylaxis who are treated with BB or ACEI, with shared decision-making regarding the potential benefits and harms of concurrent VIT treatment and medication, compared to withholding either the treatment or the medication.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Question: In patients on maintenance VIT who are treated with BB or ACEI, should VIT be stopped or the medication discontinued?

Recommendation 33 (CBS): We suggest in most cases, treatment with BB or ACEI should not be changed or discontinued in patients receiving maintenance VIT.

Strength of Recommendation: Conditional

Certainty of Evidence: Moderate

The potential for increased risk of anaphylactic reactions in patients treated with BB or ACEI was first reported in relation to insect sting allergy and VIT 30–40 years ago. These early reports cited individual cases as examples of such risk but did not include any controls or data in larger populations.[363-365] Muller and Haeberli[366] recognized the importance of BB in management of cardiovascular disease and studied patients with cardiovascular disease and BB treatment who received VIT. During VIT build-up, the BB was replaced by an alternative drug in most but continued in some due to medical necessity; the BB was resumed during maintenance VIT in most cases. There were additional patients who had been started on BB during maintenance VIT. Thus, 25 patients were on BB during VIT (all with history of severe sting anaphylaxis). Systemic symptoms occurred in 12% of the patients on BB and in 11.6% of 138 patients with cardiovascular disease who were not on BB. There was also no difference in the rate of systemic reaction to stings during VIT in patients with cardiovascular disease who were or were not on BB treatment.

Concern regarding BB and ACEI treatment in patients at risk for insect sting anaphylaxis was increased by the report of Rueff et al[367] of 962 patients with a history of sting anaphylaxis (52 on BB and 42 on ACEI) that showed a significantly greater

severity of sting anaphylaxis in patients on BB (p=0.024) or ACEI (p=0.002). A similar study by Stoevesandt et al[368] found no correlation between cardiovascular medications and the severity of sting anaphylaxis. Both groups published subsequent reports on patients receiving VIT demonstrating no increased risk of systemic adverse effects in patients receiving BB or ACEI.[369-372] It is noteworthy that both Stoevesandt et al[371] and Muller and Haeberli[366] actually found a lower incidence of adverse events in patients with cardiovascular disease who were on BB or ACEI than in those who were not.

A systematic review and meta-analysis of observational studies of the relationship between anaphylaxis of all causes and use of BB and ACEI analyzed 22,313 episodes for severity and 18,101 episodes for incidence.[296] Both BB and ACEI were associated with significantly increased severity (odds ratio 2.19 and 1.56, respectively), but the incidence of anaphylaxis (odds ratio 1.40 and 1.38, respectively) was not significantly increased. The quality of evidence was low, and it was not possible to adjust for cardiovascular disease in their analysis because only 1 study had adjusted data. The authors noted that in the 3 studies that reported severity of anaphylaxis in relation to cardiovascular disease, the odds ratio for severe anaphylaxis in relation to the cardiovascular disease was 3-fold higher than the odds ratio in those receiving BB treatment and 5 times higher than the odds ratio in those on the ACEI.[296]

More recently there have been two large studies that addressed the issue of BB/ACEI in patients experiencing anaphylaxis with somewhat conflicting results. Francuzik et al[373] reported a case-control study of 12,874 cases of anaphylaxis from the European Anaphylaxis Registry that characterized 3,612 cases of venom anaphylaxis and 3,605 matched cases of non-venom anaphylaxis. The study found a higher

frequency of severe anaphylaxis and cardiovascular symptoms in patients receiving BB or ACEI, but the authors cautioned that the apparent effect of the medications correlated closely with coexisting cardiovascular disease, so that severe anaphylactic reactions could not be attributed specifically to the medications.[373] Conversely, in the first prospective observational study and largest study of its kind, Sturm et al[297] enrolled 1,425 patients with a history of sting anaphylaxis of whom 1,342 began VIT. They found that there was no increased frequency of anaphylaxis to VIT injections or to stings during VIT in 338 patients on cardiovascular medications (27.2% on antihypertensive drugs, 10.4% BB, 11.9% ACEI, 5.0% BB and ACEI) and no increased severity of anaphylaxis to the pre-VIT sting in 388 patients on BB and ACEI (odds ratio 1.14, 95% CI: 0.89–1.46, $p = 0.29$).[297] In contrast to the earlier report of Nassiri et al,[357] the data in the study of Sturm et al[297] did not show an additive effect of BB and ACEI on the frequency or severity of anaphylaxis during VIT. Although the studies by Sturm et al[297] and Francuzik et al[373] showed somewhat differing results with respect to severity of anaphylaxis in patients on BB or ACEI, they both showed that the risk of reaction related to medications correlated very closely with the risk related to cardiovascular disease and therefore could not be attributed directly to the medications. Kopac et al[374] studied biomarkers for severe insect sting anaphylaxis and found that the use of BB or ACEI were not associated with the severity of HB field-sting reactions or adverse reactions to VIT.

The accumulated evidence now supports a modified approach to patients with insect sting allergy who are treated with BB or ACEI. Prior to VIT, there may be an increased severity of reaction to a sting but not an increased chance of reaction. For

patients on VIT, there does not appear to be any increased risk associated with cardiovascular medications. It is important to acknowledge that patients with cardiovascular disease have an inherently increased risk of severe anaphylaxis, which is all the more reason to maintain treatment that is medically indicated to mitigate that risk. Thus, it is believed to be safer for these patients to remain on appropriate BB or ACEI medications rather than to discontinue these medications. Also, changing the medication may lead to increased morbidity or mortality from the underlying cardiovascular disease, which is estimated to exceed the risk of severe anaphylaxis that might result from staying on the medications. This was found to be the case in an analysis simulating the life expectancy of patients with peanut anaphylaxis and cardiovascular disease.[375] Although the prescribing physician may be consulted about the medical necessity of the BB or ACEI medication, they should only be changed if there is a different medication that is equally safe and equally effective.

Decisions regarding VIT and continuing cardiovascular medications should occur in the context of shared decision-making that includes the relative indication for VIT (severity of previous sting reaction and risk of future sting anaphylaxis), the medical necessity of the medication (e.g., post-myocardial infarction, congestive heart failure, high blood pressure, glaucoma, or migraine for BB) and its benefit and risk, the values and preferences of the patient, and the relative efficacy of non-BB or non-ACE alternatives. Underlying cardiovascular disease is recognized in the Insect Allergy Practice Parameters as one of the high-risk factors that can support the prescription of VIT and the continuation of VIT indefinitely.[239] Therefore the recommendations for insect sting allergic patients may differ from those for other immunotherapy patients.

Allergen immunotherapy

Question: Should patients who are treated with BB or ACEI initiate a course of AIT?

Recommendation 34 (CBS): We suggest use of initial AIT may be considered in patients who are treated with BB or ACEI, with shared decision-making. It would be preferable to replace the BB or ACEI, if there is an equally safe and effective alternative.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Question: In patients on maintenance AIT who are treated with BB or ACEI, should AIT be stopped or the medication discontinued?

Recommendation 35 (CBS): We suggest that patients receiving maintenance dose AIT have minimal increased risk of severe anaphylactic reaction when on BB/ACEI and may consider continuing AIT and medications based on shared decision-making.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Similar to the findings with VIT, the use of BB or ACEI in patients undergoing SLIT has not been associated with increased severity or frequency of systemic allergic

reactions.[376, 377] Beta blockers are not associated with increased frequency, however, they may increase severity of reaction in patients receiving SCIT.[371, 376, 378] In fact, in a survey of the experience and opinion of physicians, 37.1% and 47.3% report prescribing AIT in patients receiving BB and ACEI, respectively, and none reported major anaphylactic incidents during the course of treatment.[379] The clinical significance of the theoretical risk of BB has also been questioned by a study showing they were not associated with an increased need for epinephrine.[358] However, a recent systematic review and meta-analysis assessed the incidence and severity of anaphylaxis of all causes in relation to these medications. The risk of severe anaphylaxis was significantly increased (BBs: OR 2.19; 95% CI, 1.25–3.84; ACEIs: OR 1.56; 95% CI, 1.12–2.16) but the incidence of new cases of anaphylaxis was not (BBs: OR 1.40; 95% CI, 0.91–2.14; ACEIs: OR 1.3;, 95% CI, 0.39–4.86).[296] As described above, this review found a modest increase in the severity but not the incidence of anaphylaxis. Furthermore, it was not possible to adjust for underlying cardiovascular disease, and in fact, the risk of anaphylaxis was 3–5 times higher in patients with cardiovascular disease than in those taking BB/ACEI. It is important to note that although the relative risk may be increased, the absolute risk remains very small. For example, based on this review, if the frequency of any systemic reactions to AIT is about 7%, of which about 30% are severe, then the risk of severe anaphylaxis is 2.0%. If 15% of the patients are taking BB/ACEI, then the risk of severe anaphylaxis to AIT is about 1.5% in patients on no BB/ACEI, and about 2.1% in those taking BB/ACEI – a 40% higher relative risk, but still a low absolute risk. The absolute risk of anaphylaxis is lower for SLIT than for SCIT and therefore even less likely to show an increase with BB/ACEI. There is a need for an individualized risk-

benefit discussion exploring both the potential risk of the medication and the importance to the patient of the immunotherapy treatment, as well as the patient's history of anaphylaxis and associated risk factors, in the framework of the available evidence.

Planned procedures: (eg, drug desensitization, RCM administration, IVIG infusion)

Question: For planned procedures where there is a risk of anaphylaxis, should BB or ACEI be interrupted or continued?

Recommendation 36 (CBS): For planned procedures (eg, RCM, challenge/desensitization, and infusion) if the BB/ACEI cannot be safely interrupted, we suggest shared decision-making discussion of the medical necessity (benefit) of the procedure, the relative risk of anaphylaxis, the possibility of more severe reaction if the medication is continued, and the risk of stopping the medication.

Strength of Recommendation: Conditional

Certainty of Evidence: Very low

Drug desensitization is a safe and effective treatment option for patients with severe hypersensitivity to antibiotics, chemotherapies, monoclonal antibodies, and other drugs such as aspirin. There is insufficient evidence to determine the relative risk associated with BB/ACEI during these procedures. In 2 case reports of desensitization to penicillin and gemifloxacin, allergic reactions were reported to be more severe with the use of BB's and ACEI's.[380, 381] However, as in similar case reports with food allergy

and insect sting allergy, observed associations must not be confused with causation. Drug desensitization procedures are usually performed because of the lack of safe and effective alternatives to a medically-necessary treatment. Thus, any potential risk associated with concomitant medications must be viewed in the context of the risk of foregoing the procedure or the risk of stopping the medication during the procedure.

Radiocontrast media are agents given to increase the contrast in an imaging study to allow visualization of internal structures. Similar to other causes of anaphylaxis, there has been conflicting evidence about whether BB and/or ACEI increase the frequency or severity of anaphylaxis after RCM administration. In a case control study by Lang et al[382] BB were associated with increased risk of bronchospasm or hospitalization; however, the risk of life-threatening reaction was associated with the presence of cardiovascular disorders but not with the BB. A more recent case control study of patients receiving low-osmolarity contrast for cardiac catheterization found that patients treated with BB or ACEI did not have increased frequency or severity of anaphylactic reactions.[361] In that study of 71,782 cardiac catheterizations cases, neither cardio-selective BBs (P = 0.2) nor non-cardio–selective BBs (P = 0.5) influenced adverse reaction severity.[361]

Anaphylaxis can occur during IVIG infusions; however, this is a very rare complication.[383, 384] Patients receiving their initial IVIG treatment are considered at higher risk for adverse events and should be monitored closely at the slower than usual infusion rate.[385] In a study of patients with idiopathic inflammatory myopathy and concomitant heart failure, 75% of patients receiving IVIG therapy were using BB and ACEI. In these patients, no cases of anaphylaxis were reported.[384] Literature on the

relative risk of anaphylaxis in patients receiving IVIG while on BB or ACEI is not available.

Patients at risk for anaphylaxis (unplanned exposure or unknown cause)

Question: In patients at significant risk for recurrent and unexpected anaphylaxis due to unplanned exposure or unknown cause, should BB or ACEI be stopped or continued?

Recommendation 37 (CBS): We suggest that all patients at significant risk for recurrent and unexpected anaphylaxis (e.g., those with confirmed severe food allergy, those with mastocytosis or MCAS, or with recurrent IA) should be counseled about the theoretical risk of more severe anaphylaxis, and should avoid, where possible, the use of non-selective BB or ACEI.

Strength of Recommendation: Conditional

Certainty of Evidence: Moderate

Some conditions are associated with greater frequency or severity of anaphylactic reactions, often at unpredictable times. Such patients should be counseled to take special measures to mitigate this risk, with increased caution regarding contributing factors (e.g., alcohol, vigorous exercise, medications), increased vigilance for the earliest signs of the beginning of a reaction, and ready availability of treatment with epinephrine. This may apply to patients with IA, underlying mast cell disorders, severe food allergy, or severe insect sting allergy (prior to VIT). There could reasonably be increased concern in these patients for the potential risk associated with BB or ACEI.

Idiopathic anaphylaxis is a diagnosis of exclusion and is based on the inability to identify a causal relationship between a trigger and an anaphylactic event.[386] Every effort should be made to identify a specific cause and any contributing factors or medications so as to improve further management and risk reduction. There are no specific reports on the effects of BB or ACEI in patients with IA, but the known increase risk of severe reactions that has been associated with BB/ACEI in anaphylaxis of all causes would be of concern in patients with recurrent and unpredictable anaphylaxis. As in other patients, the medical risk of changing or stopping the medication must be weighed against the risk of more severe anaphylaxis if the medications are continued.

Patients with severe food allergy have a greater chance of unexpected severe reactions. An evidence review and meta-analysis of risk factors for severe reactions in food allergy noted that although BB or ACEI may increase severity, they are less important than age as a risk factor for severe anaphylaxis.[387] Tenbrook et al[375] studied a simulated cohort of adults with severe peanut allergy and underlying cardiovascular disease. This study developed a Markov Model for patients with heart disease at risk for peanut anaphylaxis to compare their estimated life expectancy with and without BB. For people with post-myocardial infarction or congestive heart failure, the benefits of BB treatment outweighed the potentially increased likelihood of dying from anaphylaxis, increasing estimated life expectancy by 9.4 and 17.4 months, respectively. Quality of life outcomes were not evaluated.[375] Further, with the assumptions in this model, BB were preferred unless the annual rate of moderate to severe anaphylaxis exceeded 6.0% for post-myocardial infarction and 15% for congestive heart failure patients. The frequency of anaphylaxis may be of consideration in patients with frequent episodes of IA for

whom triggers are not avoidable, in contrast with food-induced anaphylaxis in which the trigger is more easily recognized.[388] Similar analyses have not been conducted for IA, MCAS, alpha-gal allergy, or HαT. Overall, before stopping BB in patients with a history of anaphylaxis, the relative risk of the cardiovascular disease without BB treatment must be weighed against the risk of more severe anaphylaxis while on BB treatment [389] and requires a shared decision-making discussion.

Summary of recommendations for BB/ACEI

In summary, clinicians should weigh the potential benefits and harms when considering the use of BB and ACEI in patients at risk for anaphylaxis. These medications are associated with an increased relative risk that any anaphylactic reaction will be more severe, although the absolute risk of severe anaphylaxis remains small and the risk of stopping or changing the medications may be greater than the risk of continuing them during any planned treatment or procedure. The risk of severe anaphylaxis may be related more to age and underlying cardiovascular conditions than to the BB/ACEI medications. In general, however, one should not assume automatically that these medications are absolutely contraindicated in this population. The discussion should include the prescribing physician (e.g., cardiologist).

Patients taking BB or ACEI who are at risk for sting anaphylaxis but are not on VIT should be counseled about the increase in relative risk (but only a small increase in absolute risk) of a sting reaction being more severe and should discuss with the prescribing clinician whether alternative medications are equally safe and effective for their treatment. For patients on maintenance immunotherapy (VIT, SCIT, or SLIT), the risk of BB/ACEI therapy is minimal and no change in medication is needed. Patients

who need to begin VIT should be counseled about the increase in relative risk (but only a small increase in absolute risk) of a reaction to VIT injection during initial build-up being more severe and the potential risks of the alternatives (changing the medications or foregoing VIT). For patients who wish to begin SCIT, the severity and history of their allergies, alongside the efficacy of alternative pharmaceutical agents, should be considered when determining whether to proceed with SCIT and whether BB and ACEI are suitable treatment options. Patients at risk for anaphylaxis from known exposures or unknown/unplanned exposures or procedures should be counseled about the increase in relative risk (but only a small increase in absolute risk) of a reaction being more severe and should discuss with the prescribing clinician whether alternative medications are equally safe and effective for their treatment. Knowledge gaps related to use of BB or ACEI in patients at risk for anaphylaxis are listed in **Table XXIV**.

Table XXIV: Knowledge gaps related to use of BB or ACEI in patients at risk for anaphylaxis.

- The true increased risk of more severe or treatment refractory anaphylaxis related specifically to treatment with BB or ACEI is unknown.
- How much is the degree of severity of anaphylaxis experienced by patients related specifically to their underling cardiovascular disease as opposed to their medication(s)?
- Is there a difference in risk of anaphylaxis associated with selective BBs versus non-selective BBs?
- Is there a difference in risk of anaphylaxis associated with ACEIs versus ARBs?
- Does the risk depend on the cause of reaction or route of exposure?
- Is the efficacy of epinephrine reduced by BB?

Mast Cell Disorders and Anaphylaxis

Mastocytosis is a clonal disorder of mast cell proliferation and is associated with episodic and chronic mast cell activation symptoms in the majority of patients.[390] Mast cell activation may present with anaphylaxis in its most severe form. It has been estimated that approximately 40–50% of adults and 10% of children with mastocytosis are at risk for anaphylaxis.[391] Risk factors for anaphylaxis associated with mastocytosis include male sex, total serum IgE >15 kU/L, atopic background, and tryptase levels less than 42 ng/mL.[392] New potential biomarkers for risk of anaphylaxis in patients with mastocytosis have been reported.[393] Anaphylaxis is also overrepresented in patients with mastocytosis who lack skin lesions; however, it is not clear if this finding is due to referral bias. The majority of anaphylaxis episodes associated with mastocytosis do not have a single identifiable trigger and sometimes may be termed “unprovoked”. In patients with mastocytosis, Hymenoptera venom allergy is the leading cause of IgE-mediated anaphylaxis in studies from Europe.[394, 395] The prevalence of drug, food, and perioperative anaphylaxis is also slightly increased in mastocytosis.[396]

Epidemiology, classification and diagnosis

Question: What is the role of bone marrow biopsy and serum tryptase level in evaluation of patients for possible mastocytosis?

Recommendation 38 (CBS): We recommend clinicians should order a bone marrow biopsy with staining for tryptase, CD25 immunohistochemistry and flow cytometry, and the KIT D816V mutation when there is strong suspicion for systemic mastocytosis.

Strength of Recommendation: Strong

Certainty of Evidence: Moderate

Recommendation 39 (CBS): We recommend clinicians should not rely on serum tryptase levels alone for diagnostic assessment of the likelihood that a patient does or does not have a clonal mast cell disorder.

Strength of Recommendation: Strong

Certainty of Evidence: Moderate

Updated classification and diagnostic criteria from the World Health Organization for cutaneous and systemic mastocytosis are detailed in **Table XXV**.[397-399] Diagnosis requires at least 1 major and one minor, or three of the 4 minor criteria. A bST in excess of 20 ng/mL is considered a significant contributory finding to the diagnosis but must be supported by additional findings.[397] Differential diagnoses of conditions which can be associated with elevated bST levels are is listed in **Table XXVI**, and the clinician should be aware that this marker is not specific for a mast cell disorder.[397, 400] Moreover, there should be awareness that the differential diagnosis of an elevated bST includes HαT, which is an autosomal dominant genetic variant caused by increased copy numbers of alpha tryptase genes encoded by TPSAB1 locus.[85] Although the clinical significance of HαT is not fully understood, it may increase the frequency and/or severity of anaphylactic reactions. HαT is observed in 5–7% of the general population and is most commonly asymptomatic but is reported in more than 15% of patients with IA, mastocytosis, or insect sting anaphylaxis.[92, 401] It is not clear whether this is due to

selection bias or a yet to be defined mechanism affecting mast cell proliferation or activation. HαT is discussed in more detail in the section on Diagnosis.

Table XXV: Proposed refined major and minor SM criteria. Reproduced from Valent et al 2021[397] under Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND).

Major criterion:	Multifocal dense infiltrates of mast cells (≥15 mast cells in aggregates) in bone marrow biopsies and/or in sections of other extracutaneous organ(s)
Minor criteria:	a. ≥25% of all mast cells are atypical cells on bone marrow smears or are spindle-shaped in mast cell infiltrates detected in sections of bone marrow or other extracutaneous organs[a] b. KIT-activating *KIT* point mutation(s) at codon 816 or in other critical regions of *KIT*[b] in bone marrow or another extracutaneous organ c. Mast cells in bone marrow, blood, or another extracutaneous organ express one or more of: CD2 and/or CD25 and/or CD30[c] d. bST concentration >20 ng/mL. In the case of an unrelated myeloid neoplasm, an elevated tryptase does not count as an SM criterion. In the case of a known HαT, the tryptase level should be adjusted[d] If at least 1 major and 1 minor or 3 minor criteria are fulfilled, the diagnosis is SM

bST, baseline serum tryptase; HαT, hereditary α-tryptasemia; SM, systemic mastocytosis.

[a] In tissue sections, an abnormal mast cell morphology counts in both a compact infiltrate and a diffuse (or mixed diffuse + compact) mast cell infiltrate. However, the spindle-shaped form does not count as an SM criterion when mast cells are lining vascular cells, fat cells, nerve cells, or the endosteal-lining cell layer. In the bone marrow smear, an atypical morphology of mast cells does not count as SM criterion when mast cells are located in or adjacent to bone marrow particles. Morphologic criteria of atypical mast cells have been described previously.[399]

[b] Any type of *KIT* mutation counts as minor SM criterion when published solid evidence for its transforming behavior is available. A list of such *KIT*mutations (including variants in *KIT* codons 417, 501–509, 522, 557–560, 642, 654, 799, 816, 820, 822) is provided in Supplemental Digital Content, Table S6, http://links.lww.com/HS/A201 (KIT-activating mutations are labeled in bold).

[c] All 3 markers fulfill this minor SM criterion when expression in mast cells can be confirmed by either flow cytometry or by immunohistochemistry or by both techniques.

[d.] Although the optimal way of adjustment may still need to be defined, one way is to divide the basal tryptase level by 1 plus the extra copy numbers of the alpha tryptase gene. Example, when the tryptase level is 30 and 2 extra copies of the alpha tryptase gene are found in a patient with HαT, the HαT-corrected tryptase level is 10 (30/3 = 10) and thus is not a minor SM criterion.

Table XXVI: Differential diagnosis for elevated baseline serum tryptase. Reproduced from Valent et al 2021[397] under Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND)

• Systemic mastocytosis
• Hereditary α-tryptasemia
• Mast cell activation syndrome
• Anaphylaxis
• Complement (and mast cell) activation-related pseudoallergy
• Myeloid neoplasm
• Helminth infection
• Renal failure
• Hypereosinophilic syndrome

A bone marrow biopsy revealing at least 15 mast cells in aggregates is the major diagnostic criterion for diagnosis of systemic mastocytosis. Skin findings of maculopapular cutaneous mastocytosis, also known as urticaria pigmentosa (hyperpigmented macules that urticate when lightly stroked), are a hallmark of cutaneous mastocytosis but also can be present in systemic mastocytosis, although systemic forms can present with minimal or no cutaneous findings.[397] In infants, skin lesions may form blisters or bullae during disease flares especially in the first 3 years of life. Other skin findings such as pruritus, urticaria, and flushing have been observed. Mastocytomas in children can resemble flesh-colored to slightly-pigmented nodules and are considered a benign mast cell tumor, which can also urticate upon being rubbed. Documentation of a thorough skin exam with pertinent positive and negative findings is of high importance.[397]

Key presenting symptoms of systemic mastocytosis will overlap with anaphylaxis but also may include the aforementioned skin findings, pre-syncope/syncope, constitutional symptoms (e.g., fevers, weight loss, night sweats), bone pain, and prominent gastrointestinal symptoms like reflux, nausea, vomiting, diarrhea, and colic. On physical exam, hepatosplenomegaly and lymphadenopathy may be prominent especially in patients with advanced disease. Multiple reviews detail the key presenting features of mast cell disorders.[390, 397, 398, 402] Systemic mastocytosis can present in childhood in approximately 10% of the cases and should remain in the differential if the child presents with the constellation of symptoms detailed above, displays increasing tryptase levels, and the cutaneous lesions fail to regress by puberty.[403-405]

The decision to recommend bone marrow biopsy in a patient presenting with anaphylaxis is not always straightforward. Decision-making and scoring schemes for bone marrow biopsy are discussed in more detail in the Diagnosis section. However, the procedure is necessary to document the key marrow pathology that defines the condition as well as for staging to determine if the disease is advanced. While mast cell proliferation can be noted in most other affected organs, the marrow remains the most important area for biopsy.[398] The clinician may consider other less invasive tests such as a blood count (looking for evidence of cytopenia and/or eosinophilia), blood chemistry (looking for other evidence of end-organ dysfunction), a bST (which is often but not always elevated in mastocytosis), or a peripheral blood KITD816V mutation analysis before deciding on a bone marrow biopsy.[96, 406] A KIT mutation analysis is also generally ordered with most bone marrow aspirates and is more sensitive than peripheral blood mutational analysis.[407] The KIT D816V mutation should be analyzed by

a highly sensitive test (such as allele specific PCR or digital droplet PCR) capable of detecting mutation at a 0.1% or lower allelic frequency. These assays have 80–90% sensitivity compared with bone marrow biopsy and >99% specificity. It is important to note that tests commonly employed in hematologic neoplasms based on next gen sequencing are not sufficiently sensitive.[407] Nonetheless, in a patient with symptoms suspicious for systemic mastocytosis, irrespective of a normal tryptase level, a bone marrow biopsy is necessary to definitively rule in or rule out the diagnosis. Clinicians ordering a bone marrow biopsy should ask for staining for tryptase, CD25 immunohistochemistry and flow cytometry, the KIT D816Vmutation using a highly sensitive allele specific PCR or digital droplet PCR based technique, and if there is peripheral eosinophilia, a FIP1L1-PDGRA mutational analysis.[397, 398]

Mastocytosis, Hymenoptera anaphylaxis, or idiopathic anaphylaxis

Question: When should bST be measured?

Recommendation 40 (CBS): We recommend measurement of bST in: patients with severe insect sting anaphylaxis, particularly those who had hypotension and/or absence of urticaria; in all cases of recurrent unexplained anaphylaxis; and in patients with suspected mastocytosis.

Strength of Recommendation: Strong

Certainty of Evidence: Moderate

Question: When should patients be evaluated for mastocytosis?

Recommendation 41 (CBS): We suggest clinicians consider evaluation for mastocytosis, including a bone marrow biopsy, for adult patients with severe insect sting anaphylaxis or recurrent IA, particularly those with a predictive REMA score.

Strength of Recommendation: Conditional

Certainty of Evidence: Moderate

Question: Should patients with mastocytosis and insect sting allergy be treated with VIT?

Recommendation 42 (CBS): We suggest VIT in patients with mastocytosis and insect sting anaphylaxis should be continued indefinitely in such patients due to the increased risk of severe or fatal sting anaphylaxis if VIT is discontinued.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Anaphylaxis to insect stings has shown a unique association with mastocytosis.[408] An unusually high frequency of clonal mast cell disorders has been found in patients with severe sting anaphylaxis.[409, 410] Venom anaphylaxis in patients with mastocytosis is associated with a unique clinical pattern of reaction and with a unique phenotype of mastocytosis.[411, 412] The frequency and clinical characteristics of mast cell disorders in patients with insect sting allergy in the US may differ from those in European reports.[413] The presentation of insect sting allergy that is most suspicious for mastocytosis is a male who develops rapid onset hypotensive shock with no urticaria.

Insect stings are the most common cause of anaphylaxis in patients with mastocytosis. In one report, patients with mastocytosis who had positive tests for venom-IgE had a very high-risk (93%) of severe and life-threatening anaphylaxis to insect stings.[414] This led the authors to suggest that testing for venom-IgE should be considered in all patients with mastocytosis and that those with positive tests should be offered VIT (even if they have never had a systemic reaction to a sting).[414] However, there is no consensus among the experts regarding preemptive VIT, and prospective confirmation of this observation is needed.

Early reports noted that elevated bST is unusually common in patients with insect sting anaphylaxis.[415-417] Recent studies suggest that in patients with insect sting anaphylaxis, bST levels greater than 8 ng/ml indicate increased risk of severe anaphylaxis to stings and suggest an underlying mast cell disorder.[418] Such patients should be monitored for possible progressive increase over a period of years in serum tryptase levels. HαT is also found in a much higher proportion of patients with sting anaphylaxis (10–20%) than in the general population (6%)[92]. However, one study found venom anaphylaxis correlated with presence of D816V mutation positive clonal mast cells rather than HαT.[406]

Although once considered too dangerous, VIT is now recommended in mastocytosis patients with insect sting anaphylaxis.[239, 395] Treatment with VIT reduces the frequency and severity of reactions to stings in patients with mastocytosis although not as efficiently as in other patients with insect sting allergy.[419] During maintenance VIT, systemic reactions to stings occur in 5–15% of patients without mastocytosis but in 25% of patients with mastocytosis.[420] This still represents significant benefit because

without VIT the risk of sting reactions in patients with mastocytosis is more than 75%.[414] There is also a higher frequency of systemic reactions to VIT injections in patients with mastocytosis (15%) than in those without mastocytosis (5%), and reactions can occur even during maintenance VIT.[421] In patients who have repeated reactions to VIT, omalizumab has been reported to enable most patients to achieve maintenance dose.[422, 423] Mastocytosis is also associated with increased risk of relapse if VIT is discontinued, with severe and even fatal sting reactions despite completing the usual 5 year course of treatment.[414, 419, 424] It is therefore recommended that patients with mastocytosis should continue VIT indefinitely.[239, 395]

Clinical presentation

Anaphylaxis manifestations in mastocytosis commonly include hypotension, syncopal or presyncopal episodes, flushing, tachycardia and gastrointestinal symptoms such as cramping, diarrhea, nausea, and vomiting. In contrast, urticaria, angioedema, and wheezing are not observed frequently.[94] All such patients should have a careful skin examination to look for the presence of maculopapular cutaneous lesions of mastocytosis (formerly known as urticaria pigmentosa), although absence of maculopapular cutaneous lesions does not rule out mastocytosis. As described in the Diagnosis section (and

Figure 4), risk-stratification schemes for the probability of mastocytosis in patients presenting with mast cell activation symptoms have been proposed by REMA and by NICAS.[94, 95, 97] According to the REMA scheme, patients with a total score of 2 or greater have a high likelihood of having systemic mastocytosis (sensitivity 0.92,

specificity 0.81) and should be considered for bone marrow biopsy and aspiration. The NICAS scoring system did not include patients with insect anaphylaxis whereas the REMA system included all causes.

Tryptase level is the most reliable surrogate marker of systemic mast cell burden and should be determined in all patients suspected of having mastocytosis. A normal median tryptase level is approximately 4.5-5 ng/mL in the general population. Elevated bST levels can be seen in chronic renal failure, myeloid disorders, and HαT. While a cutoff level of “normal” tryptase level has been suggested as 11.4 ng/mL in most commercial diagnostic tests, individuals without an extra allele of TPSAB1 encoding alpha tryptase generally have tryptase levels of <8 ng/mL.[425] See the Diagnosis section for further discussion of serum tryptase testing.

More than 90% of patients with systemic mastocytosis have a somatic activation mutation in KIT gene in a single codon (D816V).[426] Detection of this mutation in peripheral blood is a marker of clonal mast cell disease (mastocytosis) and should be considered in patients presenting with recurrent anaphylaxis, especially associated with hypotension. There are several assays commercially available to measure this mutation; as mentioned above, the most accurate results are obtained by a high sensitivity PCR droplet digital assay with a lower limit of detection of at least 0.1%.

Mast cell activation syndromes

These syndromes are comprised of a broad range of disorders with various etiologies presenting with systemic mast cell activation. They can be classified as primary (clonal; e.g., mastocytosis), secondary (IgE-mediated) or idiopathic. Mast cells are the primary

cause of anaphylaxis in humans, and therefore, IA is a prototypical MCAS. Other presentations of mast cell activation not meeting the clinical definition of anaphylaxis are also included in MCAS. In patients who otherwise do not fulfill the clinical definition of anaphylaxis, a logical approach to diagnosis has been proposed to include 3 diagnostic criteria, all of which should be fulfilled:

1. Symptoms consistent with mast cell activation in at least 2 different organ systems (cardiovascular, respiratory, naso-ocular, gastrointestinal, cutaneous),
2. Documentation of elevated mast cell mediator levels during an episode (most specific marker is tryptase, and threshold levels have been described [see Diagnosis section] for the minimal diagnostic increase in a post-event tryptase obtained within 4 hours), and
3. Positive response to mediator-targeting drugs.[81, 427, 428]

Chronic and nonspecific multi-organ symptoms and patients with multiple environmental and food intolerances without meeting these criteria should not be diagnosed with MCAS.

Special treatment considerations of anaphylaxis in mastocytosis

Omalizumab

There has been much interest in omalizumab as a potential therapeutic for patients who have recurrent anaphylaxis due to mastocytosis. Omalizumab reduces the risk of anaphylaxis during rush immunotherapy for ragweed and Hymenoptera venom and during immunotherapy for food allergy. A randomized clinical trial showed a promising trend, but results were not significant in a small group of 19 patients with severe IA.[429] A systematic review identified 12 studies with 35 subjects with IA treated with omalizumab: 63% had a complete response and 28.5% had a partial response.[430]

Most studies have used omalizumab dosing similar to that used for chronic idiopathic urticaria.

In patients with mastocytosis there are reports of improved control of symptoms and prevention of anaphylaxis with omalizumab.[431-433] Carter et al[434, 435] reported on successful control of anaphylaxis in 2 patients, with sustained results in long-term (12 year) follow-up. A recent systematic review found a total of 69 mastocytosis patients treated with omalizumab (13 cutaneous and 56 systemic). There was greater improvement in prevention of anaphylaxis (84%) than in other systemic symptoms (improved in 0–43%).[436]

Omalizumab is not currently FDA-approved in the US for this indication, and further well-designed studies are needed, but off-label prescription may be considered in patients with mastocytosis who have frequent episodes of anaphylaxis despite optimal medical treatment. However, when there are signs of increasing mast cell burden and uncontrolled symptoms, other treatment modalities, particularly kinase inhibitors, are more likely to be effective.

Mast cell cytoreduction and tyrosine kinase inhibitors

There is evidence that mast cell cytoreduction results in improvement of anaphylaxis in mastocytosis. In one study, use of cladribine (an anti-metabolite purine analog) for advanced and indolent mastocytosis resulted in complete clearance of anaphylactic episodes.[437] D816V KIT mutation associated with mastocytosis results in constitutive activation of the tyrosine kinase function of the molecule. As such, tyrosine kinase inhibitors (TKIs) targeting D816V KIT have been considered a first line approach for mast cell cytoreduction, given toxicities associated with cladribine. While

cytoreductive therapy has been traditionally reserved for patients with advanced mastocytosis, recent emergence of TKIs with low toxicity profiles have made this treatment an attractive possibility for those presenting with mast cell activation symptoms inadequately controlled with symptomatic therapies.[438] Midostaurin and avapritinib are the TKIs currently FDA-approved for treatment of advanced mastocytosis associated with decreased life expectancy (i.e., aggressive systemic mastocytosis, systemic mastocytosis with an associated hematological neoplasm, and mast cell leukemia), and their mast cell cytoreductive effects are associated with symptom control of mast cell activation.[439-441]

Midostaurin is a multi-kinase inhibitor whose targets include wild type and D816V mutated KIT. It has been shown to resolve anaphylactic episodes in 3 of 4 patients (75%) at 3 months and 2 of 2 patients (100%) at 6 months in patients with advanced systemic mastocytosis.[442] It should be noted that these drugs require periodic monitoring with CBC with differential and CMP. An open label trial of midostaurin in indolent systemic mastocytosis showed significant reduction of symptoms due to mast cell activation, but nausea and vomiting are common adverse effects of the drug.[443]

Avapritinib, a selective D816V KIT inhibitor, has recently been approved by the FDA for treatment of patients with advanced systemic mastocytosis.[440, 441] Its use has been associated with mast cell cytoreduction and improvement in mast cell activation symptoms including a case report describing successful cessation of recurrent anaphylaxis.[444] Avapritinib is currently in clinical trial for indolent systemic mastocytosis (ClinicalTrials.gov Identifier: NCT03731260) with preliminary results showing reduction of mast cell activation symptoms at all tested dose levels.[445] Other KIT D816V selective

TKIs currently being evaluated in clinical trials include BLU-263 (NCT04910685) and bezuclastinib (NCT05186753). In patients with mastocytosis and recurrent episodes of anaphylaxis despite optimal medical therapy with high dose H1-antihistamines and H2-antihistamines (and possibly a trial of omalizumab), consideration may be given to compassionate use of midostaurin or avapritinib, or referral to a clinical trial for a tyrosine kinase inhibitor, although neither is currently FDA-approved specifically for prevention of anaphylaxis.

Knowledge gaps related to anaphylaxis in mastocytosis are listed in **Table XXVII**.

Table XXVII: Knowledge gaps related to anaphylaxis in mastocytosis.

- What are the mechanisms of mast cell activation in mastocytosis, and why are certain clinical presentations (such as hypotension) more prevalent than others (such as urticaria and angioedema)?
- Are TPSAB1 copy number variations truly a modifying factor of severity of mastocytosis, and if so, what are the mechanisms for it? To avoid selection bias, prospective studies should be designed in which basal tryptase levels are not known at the time of patient recruitment.
- Can D816V KIT tyrosine kinase inhibitors be used as a prophylactic strategy in patients who have mastocytosis with recurrent anaphylaxis refractory to or intolerant of maintenance anti-mediator therapies?
- Is VIT indicated in patients with a history of venom anaphylaxis and negative IgE testing? If so, to which venoms?
- Is prophylactic venom testing (and VIT if positive) indicated in all patients with mastocytosis?
- What is the diagnostic sensitivity of high sensitivity peripheral blood D816V KIT mutation testing as a screening strategy for underlying mastocytosis in different clinical scenarios and basal tryptase levels?
- Are new treatment modalities effective to prevent anaphylaxis?

TPSAB1, tryptase α/β-1; VIT, venom immunotherapy.

Perioperative Anaphylaxis

Perioperative anaphylaxis occurs at a rate of 15.3 per 100,000 cases, is associated with increased cost and prolonged length of hospital stay, and can result in 2% excess mortality.[446] POA has a greater risk of death than other forms of anaphylaxis.[447, 448] In a multivariate analysis of POA cases, independent risk factors associated with a fatal outcome related to NMBAs, despite treatment with epinephrine, were: male sex (female sex: OR = 0.4; 95% CI, 0.2–0.7; *P* = 0.0004), emergency setting (OR = 2.6; 95% CI, 1.5–4.6; *P* = 0.0007), history of hypertension (OR = 2.5; 95% CI, 1.5–4.4; *P* = 0.0010) or other cardiovascular disease (OR = 4.4; 95% CI, 2.4–8.1; *P* < 0.0001), obesity (OR = 2.4; 95% CI, 1.1–5.3; *P* = 0.0376), and BB exposure (OR = 4.2; 95% CI, 1.8–9.8; *P* = 0.0011).[449] Increased risk for POA has also been associated with transplant, cardiac, vascular, and hematologic procedures.[446] Recent trends in POA include the recognition of geographic variation in etiologic agents (perhaps based on different pre-procedure exposures to sensitizing factors), a declining incidence of POA due to latex, and a greater appreciation for reactions related to antibiotics – particularly cefazolin.[450-452] It is important to note that rigorous evidence on this topic is lacking due to the limitations resulting from the relatively rare occurrence of POA and inability to perform double-blind studies due to ethical considerations. Therefore, the strength of evidence is uniformly low to very low.

POA is usually due to immunologic or non-immunologic activation of mast cells and, to a lesser extent, basophils. Measurement of mast cell mediators, particularly more stable mediators such as tryptase, is a validated strategy to confirm involvement of mast cell degranulation in the pathogenesis of POA.[451, 452] A retrospective study

demonstrated that serious anaphylaxis during anesthesia was associated with elevations in serum tryptase (mean = 86.5 ng/mL); moreover, tryptase elevation was not observed in a comparator group with cardiogenic or septic shock who were resuscitated.[451] These data imply that resuscitation itself cannot account for serum tryptase elevation. However, serum tryptase is not always increased in anaphylaxis, even in severe or fatal reactions. A French study of POA reported an increase in serum tryptase in 68% of suspected IgE-mediated POA but in only 4% of non-IgE-mediated POA.[453] Elevations in serum tryptase are most often detected in cases of anaphylaxis that involve hypotension and in reactions that are IgE-mediated.[24, 446, 450, 453] The sensitivity (64%) and specificity (89%) of elevated serum tryptase (>11.4 ng/mL) leads to a calculated positive likelihood ratio (LR) of 6 and a negative LR of 0.4. These LRs indicate that an elevated serum tryptase gives moderate support to the likelihood of POA, but a lack of increase in serum tryptase should not be interpreted as ruling out a diagnosis of POA.

Assay of plasma histamine to confirm a diagnosis of anaphylaxis is generally not recommended as this is complicated by the rapid degradation and decline of blood values following POA; however, in the rare circumstance in which a blood sample is obtained within 30 minutes of POA, a plasma histamine determination may be of value.[24, 453]

Interpretation of serum tryptase is based upon international consensus recommendations noting a 1.2-fold increase plus 2 ng/ml, consistent with degranulation of mast cells during the suspected reaction.[425] Because bST values may be more variable in patients with mastocytosis or HαT, one study found optimal sensitivity and

specificity with a threshold acute/baseline tryptase level of 1.685 (further discussed in the Diagnosis section).[82] The timing of obtaining the serum sample is important. The concentration peaks within 30–60 minutes of the reaction and then typically returns to baseline over approximately 120 minutes (but up to 4 hours or more). Interpretation of tryptase levels obtained in proximity to death or postmortem may be unreliable as nonspecific increases occur during ischemia.[454] Tryptase is stable for as long as one year if a blood sample is frozen after processing. This could enable retrospective investigation of suspected POA.

A 15-year Belgian survey identified 180 subjects with tryptase determinations from a total of 532 subjects with POA;[455] in 139 (77%) with clinical POA, an increase of tryptase (greater than 1.2 x baseline + 2 mcg/L) was observed. Severity of anaphylaxis was associated with a tryptase exceeding the aforementioned threshold (11.4 ng/mL), but the severity of POA did not correlate with the absolute tryptase value. Furthermore, an increase in tryptase did not correlate with the identification of a culprit-drug specific IgE. Thus, the finding of elevated mast cell mediators implies that mast cell/basophil degranulation occurred, although it does not provide information regarding the underlying mechanism of the reaction (i.e., IgE-mediated or non-IgE–mediated). A number of perioperative drugs, including paralytics (NMBAs), opioids and antibiotics (e.g., vancomycin), can induce mast cell degranulation independent of IgE.[24, 451, 452, 456] To determine whether serum tryptase is increased following POA, a repeat measurement should be performed when the patient has recovered to provide a baseline tryptase level for comparison with the acute level and to determine whether tryptase levels are persistently increased.[425] The baseline level should be determined

even if the acute phase tryptase is normal. Diagnostic evaluation of patients with persistent elevations of tryptase is discussed further in the Diagnosis section and the Mast Cell Disorders section.

Question: Should immediate hypersensitivity skin testing or in vitro testing be performed with all potential culprit pharmacologic and non-pharmacologic agents, or should this be limited to the agents that are highly suspected?

Recommendation 43 (CBS): We suggest that immediate hypersensitivity skin testing (percutaneous and intradermal) and/or in vitro specific-IgE testing should be performed, when available, to all potential pharmacologic and non-pharmacologic culprits used during the perioperative period.

Strength of Recommendation: Conditional

Certainty of Evidence: Very low

POA is complicated by the fact that multiple agents are usually administered simultaneously or in close succession. Epidemiologic evidence supports the assertion that antibiotics and paralytics (NMBAs) are the more common culprits,[450, 452] but the limited reliability and validity of testing to these agents makes it incumbent to consider all potential causes.

Depending on history or clinical suspicion is not reliable. When referring anesthetists at a Danish Anesthesia Allergy Center were asked to provide their pre-testing causes for POA, these were not confirmed in 73% of cases, resulting in a poor correlation between clinical impression and the results of diagnostic evaluation.[457] These data imply that testing for *all* potential culprits is required in the evaluation of

patients with POA. Also, testing for available alternatives to highly suspected culprit agents may be considered. Because NMBAs are among the most common causes of POA and to reduce the need for follow-up testing, the tests should include the potential culprit NMBA as well as any alternative NMBAs agents available at that health-care facility.

Published resources provide empirical, non-irritating concentrations for hypersensitivity skin testing of potential culprit pharmacologic causes of POA, as shown in **Table XXVIII**.[458] The positive and negative likelihood ratios of such testing have not been determined. A positive skin test result implies greater risk for IgE-mediated reaction with re-exposure, although this has not been established, and non-IgE mechanisms can cause positive skin test responses. Immediate hypersensitivity skin testing to direct mast cell activators, such as opioids or vancomycin, may be unreliable due to high rates of false positive results. Avoidance of drugs showing a positive skin test would likely be in a patient's best healthcare interest, if equally efficacious, structurally unrelated alternatives are available. Data demonstrate that administration of agents with negative test results can proceed safely, suggesting that testing may be helpful in drug selection for subsequent anesthesia (**Table XXIX**).[459-461] Just as we do with many other allergens to which skin testing is negative (e.g., latex, lidocaine, chlorhexidine, povidone-iodine), as the sensitivity (or negative likelihood ratio) are not well established, we may carry out provocative challenges to definitively rule out IgE-mediated (allergic/anaphylactic) potential. For some agents (e.g., NMBAs, midazolam, propofol), it would be appropriate for an anesthesiologist to administer them in a graded dose (i.e., "test dose") fashion immediately prior to the planned procedure.

Table XXVIII: Recommended concentrations for skin tests: Skin prick tests and intradermal tests. Reproduced from Laguna et al 2018.[458]

	SPT Concentration	IDT Concentration
NMBAs		
Atracurium	1 mg/mL	0.01 mg/mL
Cisatracurium	2 mg/mL	0.02 mg/mL
Mivacurium	0.2 mg/mL	0.002 mg/mL
Pancuronium	2 mg/mL	0.2 mg/mL
Rocuronium	10 mg/mL	0.05 mg/mL
Vecuronium	4 mg/mL	0.4 mg/mL
Suxamethonium	10 mg/mL	0.1 mg/mL
Hypnotics		
Etomidate	2 mg/mL	0.2 mg/mL
Ketamine	10 mg/mL	1 mg/mL
Propofol	10 mg/mL	1 mg/mL
Thiopental	25 mg/mL	2.5 mg/mL
Midazolam	5 mg/mL	0.5 mg/mL
Opioids*		
Alfentanil	0.5 mg/mL	0.05 mg/mL
Fentanyl	0.05 mg/mL	0.005 mg/mL
Remifentanil	0.05 mg/mL	0.005 mg/mL
Sufentanil	0.05 mg/mL	0.0005 mg/mL
Morphine	1 mg/mL	0.01 mg/mL
Sugammadex	Undiluted	1/100
β-lactams		
BPO-OL	0.04	0.04
MD	0.5	0.5
Amoxicillin	20 mg/mL	20 mg/mL
Cephalosporins	20 mg/mL	2 mg/mL
Local anesthetics	Undiluted	1/10
Heparins	Undiluted	1/10
Tranexamic acid	Undiluted	1/10
Protamine	Undiluted	1/1000 – 1/10,000
Aprotinin	1/5	1/500
Hyaluronidase	Undiluted	1/10
Antiseptics		
Chlorhexidine	5 mg/mL	0.002 mg/mL
Dyes		
Patent blue	Undiluted	1/10
Methylene blue	Undiluted	1/10

* hypersensitivity skin testing to opioids may be unreliable due to high rates of false positive results.
BPO-OL, benzylpenicilloyl; IDT, intradermal test; MD, minor determinant; NMBA, neuromuscular blocking agent; SPT, skin prick test.

Availability of drugs for testing is limited by the controlled nature of many agents used in anesthesia and distribution exclusively by in-patient pharmacies. Albeit very small amounts of the drugs are needed for testing, the acquisition of samples is often unobtainable due to geographical, logistic, and legal barriers. These issues are generally less of a problem in some integrated healthcare systems but can be very limiting in the more common scenarios of outpatient allergy/immunology clinics not affiliated with or separated from large medical centers. Based on availability and feasibility, a 3-tier recommendation may be considered:

1) testing is suggested.

2) if testing is not possible, referral to another center is suggested.

3) if referral is not possible or time-constrained, avoid the most likely culprits and use the most efficacious structurally dissimilar agents.

Question: Should immediate hypersensitivity skin and/or in vitro testing of suspected culprit (and alternative) agents be performed as soon as possible, or delayed 4-6 weeks after the POA event?

Recommendation 44 (CBS): We suggest that immediate hypersensitivity testing to suspected culprit (and alternative) agents should be delayed after POA, unless repeat surgery cannot be postponed. If surgery with general anesthesia is needed sooner, then testing should be performed as soon as possible.

Strength of Recommendation: Conditional

Certainty of Evidence: Very low

Delaying immediate hypersensitivity skin testing for 4–6 weeks following anaphylaxis is generally suggested. This is based on case series and case reports of insect allergy, drug allergy, and POA.[462, 463] Additional support for delaying the timing of skin testing after an anaphylactic event based on a “refractory period”, characterized by lack of immediate cutaneous response to a clinically relevant allergen, was provided by Goldberg and Confino-Cohen.[464] In their study, skin testing was performed within 1 week and 4–6 weeks following a Hymenoptera systemic sting reaction. In 21% of cases, the 2nd evaluation, performed 4–6 weeks later, was required to confirm the diagnosis of Hymenoptera venom anaphylaxis. This phenomenon may be due to a generalized mast cell hypo-responsiveness (a.k.a ‘the empty mast cell syndrome’) or may be allergen-specific following an anaphylactic reaction.[465]

Variability in the results of evaluation after POA is supported by a study that compared the results of skin testing at two time points in patients with POA,[466] the first within four days of the reaction and the second, four to eight weeks after POA. Of patients with positive skin test results implicating a specific drug, 15 had positive results at the first testing (4 days after POA), 22 at the second testing, 12 at both, 3 only at the first testing, and 10 only at the second testing. Based on these data, the authors recommended that until an evaluation is complete, agents statistically more likely to have caused the initial reaction, even with a single negative test, ideally should be avoided during subsequent anesthesia. Testing to any POA-related agents other than penicillin has not been clinically validated.

The limited information related to hypo-responsiveness for variable time periods after anaphylaxis coupled with the lack of validated allergy testing for most agents used

in anesthesia provides support for a recommendation to delay testing, if possible.[464-466] However, there may be a need for repeat anesthesia sooner than 4–6 weeks after the sentinel POA, especially since the procedure resulting in the POA is frequently aborted. If so, the risk of delay in testing should be discussed with the patient, anesthesiologist, surgeon, and other relevant healthcare providers to support a shared decision-making process that includes the values and preferences of the patient (and family). Another consideration would be to seek an alternative management strategy or use drugs structurally unrelated to the agents to which the patient was exposed in the POA event.

Question: Should challenges be performed to potential POA pharmacologic and non-pharmacologic culprits to which skin and/or in vitro testing is negative?

Recommendation 45 (CBS): We suggest that challenges should be performed to all culprit agents to which skin and/or in vitro testing is negative.

Strength of Recommendation: Conditional

Certainty of Evidence: Very low

Just as the reference standard for diagnostic evaluation of antibiotic allergy is tolerance of a drug challenge, usually oral,[467] similarly, the reference standard for evaluation of POA also entails carrying out challenges to items for which skin and/or in vitro testing is negative. Unfortunately, oral challenge with most perioperative agents is not feasible, potentially increasing the risk of the challenge. The lack of validated testing for all agents other than penicillin makes challenges necessary to verify tolerance. In general, suspected agents with positive testing are avoided in favor of alternative agents that are structurally unrelated or which demonstrate negative test results. Cross-

reactivity among chemically related agents, such as paralytics/NMBAs, is suspected but not documented. Direct mast cell activators, such as drugs binding to MRGPRX2, p-I receptors or other inherent activating receptors, also likely share cross-reactivity within the same class of pharmaceuticals. These include fluoroquinolone antibiotics, opioids, NMBAs, polymyxins, icatabant, vancomycin, and iopamidol RCM. Immediate hypersensitivity skin testing to direct mast cell activators, such as opioids or vancomycin, may be unreliable due to high rates of false positive results.[468]

Graded challenge with suspected agents for which skin testing is negative may also be carried out in collaboration with an anesthesiologist, and if necessary and feasible, in the OR in conjunction with a planned procedure.[469] For instance, in cases for which challenge with a NMBA is indicated, this can be performed in partnership with the anesthesiologist involved with managing the return to the operating room. This can be accomplished via administration of a 10% “test dose” prior to the procedure; if tolerated without untoward reaction after a period of observation, full dosing can then be administered as indicated.

Question: Should patients with POA be advised to avoid repeat anesthesia?

Recommendation 46 (CBS): We suggest that repeat anesthesia may proceed in the context of shared decision-making and as directed by history and results of diagnostic evaluation.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Several studies have reported that repeat anesthesia following appropriate evaluation of POA can be performed successfully with a very low rate of recurrence of POA. Fisher et al[459] reported that of 606 patients who had POA, 183 of 246 (74%) who were contactable underwent anesthesia subsequently without remarkable untoward reaction. In a study by Guyer et al[460] of 73 with POA, 47 (64%) had subsequent procedures with anesthesia; 45 tolerated these procedures without complication, the 2 who developed recurrent hypersensitivity reactions were found to have mast cell disorders. Miller et al[461] investigated 70 of 174 cases who underwent repeat anesthesia; 3 whom had recurrence of POA: 1 who was found to have a mast cell disorder, and 2 who had incomplete referral information that led to offending drugs being omitted from diagnostic testing. This report emphasizes the importance of detailed information related to the timing of drug dosing and onset of POA. As shown in **Table XXIX**, combining these three reports leads to a rate of recrudescence of POA with subsequent anesthesia of 1.7%.[459-461] These data support the contention that the majority of patients are able to undergo repeat anesthesia using a combination of skin and/or in vitro testing results, avoidance of most likely culprits, or alternative anesthesia strategies.[450]

Table XXIX: Rate of recurrence of POA.

Citation	Cases of (Suspected) POA	Contactable and Confirmed POA Cases	Cases of Subsequent Anesthesia	Procedures Performed without POA	Recurrent POA
Fisher et al 2011[459]	606	246	183	183	0
Guyer et al 2015[460]	73	73	47	45	2
Miller et al 2018[461]	174	70	70	67	3
TOTAL	**853**	**389**	**300**	**295**	**5 (1.7%)**

POA, perioperative anaphylaxis.

Question: Should repeat anesthesia following POA be performed with equally efficacious, structurally unrelated alternatives rather than the suspected culprit agents with negative skin and/or in vitro test results when challenge is not feasible?

Recommendation 47 (CBS): We suggest that avoidance of culprit pharmacologic and non-pharmacologic agents associated with POA may be considered, regardless of test results if challenge is not feasible and equally efficacious, structurally-unrelated alternatives are available.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Immediate hypersensitivity skin testing to penicillin is validated; if testing is positive to the beta lactam only, it is acceptable to use all perioperative drugs except for the beta lactam, while performing cautious challenge with agents to which skin testing was negative to validate the lack of an IgE-mediated reaction to these agents. However, the lack of validated testing for virtually all agents except for penicillin, limits the predictive value of the testing. For patient safety, if challenges are not possible or feasible, alternative agents are preferable, if available and equally efficacious. Although alternative forms of anesthesia, such as spinal or regional anesthesia, have been considered and suggested, patients still may potentially require conversion to general anesthesia, and intubation. As a result, alternative management strategies for the underlying disease process should be considered and reviewed by the anesthesiologist, surgeon, allergist/immunologist, and patient (and family). Perioperative latex avoidance

should be considered if latex is suspected as the culprit agent and diagnostic evaluation including provocative latex challenges[470] have not been performed. Latex mitigation or avoidance strategies are generally available in facilities performing general anesthesia.

Question: If all immediate hypersensitivity skin testing (percutaneous and intradermal) and/or in vitro specific-IgE testing (and challenge when possible) is negative to suspected POA culprit agents, should pre-treatment with H1 antihistamine and corticosteroid, with or without H2 antihistamine and anti-leukotriene, be administered prior to subsequent anesthesia?

Recommendation 48 (CBS): We offer no recommendation for or against the use of pretreatment prior to return to the operating room in patients with negative cutaneous (percutaneous and intradermal) and/or in vitro specific-IgE testing (and challenge when possible) to all suspected POA culprit agents.

Strength of Recommendation: None

Certainty of Evidence: Very Low

For a patient with POA and negative immediate hypersensitivity testing followed by negative provocative challenges, the recommendation as to whether to recommend pre-treatment with H1 antihistamine and corticosteroid, with/without H2 antihistamine and anti-leukotriene, prior to returning to the operating room fulfills equipoise criteria.[471] The equilibrium between pretreatment and no pretreatment implies not only balance, but also uncertainty. Based on the core principle of equipoise,[471] we must acknowledge we do not know what is best for patient care outcomes and recommend this decision be based on an individualized and careful consideration of the potential for benefit

compared with the potential for harm, and allow the patient (and family) to participate in the medical decision-making process by expressing their values and preferences.

The value of pretreatment is based upon indirect evidence, such as prevention of non-IgE–mediated anaphylaxis with re-exposure to high-osmolar radioiodinated urographic contrast in prior reactors, and prophylaxis of IgE-mediated anaphylaxis in association with rush immunotherapy.[472, 473] There is no direct evidence that premedication prevents anaphylaxis to the various factors that cause most cases of POA. There are potential harms of pretreatment that should also be considered.[2] The decision to utilize a pretreatment regimen should be based upon a shared decision-making discussion between the patient, allergist/immunologist, anesthesiologist, and surgeon.

Knowledge gaps related to perioperative anaphylaxis are listed in **Table XXX**.

Table XXX: Knowledge gaps in perioperative anaphylaxis.

Knowledge Gap
• Positive and negative likelihood ratios for skin testing to pharmacologic and non-pharmacologic agents implicated as causes of peri-operative anaphylaxis have not been determined by challenge with culprit agents.
• Necessity of avoidance of potentially 'cross reacting agents'. Can alternatives in the same chemical class be substituted with or without specific testing?
• Develop in vitro specific-IgE and basophil activation tests, and other methodologies to improve diagnostics and biomarkers of perioperative anaphylaxis.
• Improving access to culprit agents so that community practice allergy/immunology providers can perform a comprehensive evaluation.
• Optimal timing of evaluation. Additional evidence to support the value of testing in closer proximity of the event would be useful
• If the assessment of perioperative anaphylaxis is negative or not possible, it would be useful to know if any pretreatments reduce risk of POA.

- Methods for determining if non-IgE mechanisms (eg MRGPRX2) are responsible for POA and strategies for future anesthesia if non-IgE mechanisms suspected. Should all MRGPRX2 activators be avoided after POA with suspected MRGPRX2 mechanism? Does pre-treatment reduce severity of MRGPRX2-mediated anaphylaxis?

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