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Practice Parameters

Anaphylaxis: A 2023 practice parameter update

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ABSTRACT

This practice parameter update focuses on 7 areas in which there are new evidence and new recommendations. Diagnostic criteria for anaphylaxis have been revised, and patterns of anaphylaxis are defined. Measurement of serum tryptase is important for diagnosis of anaphylaxis and to identify underlying mast cell disorders. In infants and toddlers, age-specific symptoms may differ from older children and adults, patient age is not correlated with

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reaction severity, and anaphylaxis is unlikely to be the initial reaction to an allergen on first exposure. Different community settings for anaphylaxis require specific measures for prevention and treatment of anaphylaxis. Optimal prescribing and use of epinephrine autoinjector devices require specific counseling and training of patients and caregivers, including when and how to administer the epinephrine autoinjector and whether and when to call 911. If epinephrine is used promptly, immediate activation of emergency medical services may not be required if the patient experiences a prompt, complete, and durable response. For most medical indications, the risk of stopping or changing beta-blocker or angiotensin-converting enzyme inhibitor medication may exceed the risk of more severe anaphylaxis if the medication is continued, especially in patients with insect sting anaphylaxis. Evaluation for mastocytosis, including a bone marrow biopsy, should be considered for adult patients with severe insect sting anaphylaxis or recurrent idiopathic anaphylaxis. After perioperative anaphylaxis, repeat anesthesia may proceed in the context of shared decision-making and based on the history and results of diagnostic evaluation with skin tests or in vitro tests when available, and supervised challenge when necessary.

What Is New and What Is 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 an initial reaction, persistence of the reaction, and use of more than one dose of epinephrine. Baseline serum tryptase (bST) level should be measured in patients presenting with a history of recurrent, idiopathic, or severe anaphylaxis, Hymenoptera venom anaphylaxis, or with suspected mastocytosis. Evaluation for hereditary α-tryptasemia (HαT) and clonal mast cell disease should be considered if bST level is more than 8 ng/mL. 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 on 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 health care facilities. Reactions may occur at home, school, work, dining out, traveling, or in 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 the carrying and using of epinephrine autoinjectors (EAIs) and the recognition and avoidance of exposures. Childcare centers and schools should implement staff training and stock undesignated 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 require specific counseling and training of patients and caregivers, including when and how to administer the EAI and whether and when to call 911 (emergency medical services [EMS]). Health care 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 the number of EAIs to prescribe. If epinephrine is used promptly, immediate activation of the 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 after the first dose of epinephrine.

Beta-Blockers and Angiotensin-Converting Enzyme Inhibitors

Both beta-blockers (BBs) and angiotensin-converting enzyme inhibitors (ACEIs) 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 sting anaphylaxis. Venom immunotherapy (VIT) may be considered for patients receiving BBs/ACEIs, 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 BBs/ACEIs 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. The bST level 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.

Perioperative Anaphylaxis

Continued study of anaphylaxis during and after surgical anesthesia has improved the 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 perioperative anaphylaxis (POA), repeat anesthesia may proceed in the context of shared decision-making and based on the history and results of diagnostic evaluation. Immediate hypersensitivity skin testing (percutaneous and intradermal) and/or in vitro-specific IgE testing should be performed, if available, to all potential pharmacologic and nonpharmacologic culprits used during the perioperative period. If testing is not possible, we suggest referral to another center or if necessary, use of the most efficacious agents structurally dissimilar from the most likely culprit. 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 nonpharmacologic 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. Although anaphylaxis is not an infrequent occurrence, with a lifetime prevalence estimated at 1.6% to 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. 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 after an immunization. In an effort to further simplify diagnosis, the WAO created a definition with only 2 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. 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. Although 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.

Diagnosing anaphylaxis relies on a thorough clinical history that includes patient characteristics (eg, age, sex, medical and atopic history, concurrent medications), detailed description of the reaction (possible triggers, symptom pattern, timing of onset duration of symptoms), concomitant factors (eg, 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 laboratory-defined normal value (eg, >11.4 ng/mL in many laboratories) is informative, many cases of anaphylaxis may not be associated with a tryptase elevation above that level. Particularly in these situations, an acute serum total tryptase level at least 20% plus 2 ng/mL above 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 found 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 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. When foods are introduced to young children, anaphylaxis is not frequently reported as the first reaction and is far less common than mild-to-moderate, primarily cutaneous, reactions. 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 childcare 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 childcare centers and schools, there may be specific circumstances in which implementation of allergen-restricted zones (eg, milk-free table) may be appropriate, such as when there are students who lack the capacity to self-manage.

Counseling patients 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 labeling regulations (both United States and those from other countries relevant to the patient's travel plans) 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 (ie, 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 before ordering their meal, informing 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. Although airplane emergency kits in the United States contain epinephrine vials, drawing up appropriate doses using a needle and a syringe in a cramped air cabin midflight 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; IA; frequent allergen exposure through occupation or other activities (for venom, latex, drug allergy); prior systemic allergic reaction to AIT or VIT; venom allergy with honey bee as the trigger, elevated bST level, older age, underlying cardiovascular disease (CVD); 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 less than 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. Although the US Food and Drug Administration (US FDA) has approved 0.3 mg EAIs for patients weighing above or equal to 30 kg, 0.15 mg EAIs for patients weighing 15 to 30 kg, and a 0.1 mg EAI (Auvi-Q) for patients weighing 7.5 to 15 kg, multiple medical organizations (American Academy of Allergy, Asthma & Immunology [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 AAP supports the option to use the 0.1 mg dose (if available) for patients weighing 7.5 to 13 kg and the 0.15 mg dose for patients weighing 13 to 25 kg. However, the 0.1 mg EAI is not universally available, and the AAP and Joint Task Force on Practice Parameters (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 improve clinical outcomes by decreasing risk of biphasic reactions and the need for hospitalization. Therefore, epinephrine should be administered at the first sign or symptom of suspected anaphylaxis. However, there is no evidence that preemptive use of epinephrine in an asymptomatic patient will prevent anaphylaxis. Serious adverse reactions to intramuscular 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 additional EAIs. Situations that would warrant EMS activation include severe anaphylaxis, symptoms that do not resolve promptly, completely, or nearly completely, or symptoms that return or worsen.

Beta-Blockers and Angiotensin-Converting Enzyme Inhibitors

Both BBs and ACEIs have been previously considered to be contraindicated in patients at high risk for anaphylaxis because their physiological effects could theoretically increase the severity of anaphylaxis and affect the response to treatment. The BBs may reduce compensatory cardiovascular responses to anaphylaxis, enhance the release of mast cell mediators, and interfere with the effects of epinephrine. The ACEIs prevent the breakdown of bradykinin, promote vasodilation, and may have direct effects on mast cells.

With more recent data and availability of more cardioselective beta-blocking agents, shared decision-making is needed when assessing the risks of potential anaphylaxis while receiving the BBs/ACEIs, the cardiac risk of stopping the BBs/ACEIs, and alternative medications or procedures. For patients with insect sting allergy who receive BBs/ACEIs, VIT may be considered as there seems to be little or no increased risk of reaction to VIT associated with these cardiovascular medications. Similarly, AIT may be pursued in patients on BBs or ACEIs, 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 BBs/ACEIs. For planned procedures that carry a risk of anaphylaxis (eg, radiocontrast media [RCM], challenge/desensitization, and infusion), if the BBs/ACEIs 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 BBs/ACEIs are continued. Patients at significant risk for recurrent and unexpected anaphylaxis (eg, severe food allergy, mastocytosis, or mast cell activation syndrome [MCAS], or recurrent IA) should receive counseling about the theoretical risk of more severe anaphylaxis and should avoid nonselective BBs or ACEIs, if possible. There is insufficient evidence to distinguish angiotensin receptor blockers (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% to 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 sex, total serum IgE greater than 15 kU/L, atopic background, and basal tryptase levels less than 42 ng/mL. Basal tryptase levels greater than 42 ng/mL are associated with mastocytosis but are reported not to have markedly increased risk for severe anaphylaxis.

The World Health Organization (WHO) 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), presyncope/syncope, constitutional symptoms (eg, fevers, weight loss, night sweats), bone pain, and prominent gastrointestinal symptoms, such as reflux, nausea, vomiting, diarrhea, and colic. On physical examination, hepatosplenomegaly and lymphadenopathy may be prominent especially in patients with advanced disease. Although 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/or flow cytometry, the KIT D816Vmutation using a highly sensitive allele-specific polymerase chain reaction (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 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 H_1 and H_2 antihistamines, off-label treatment with omalizumab can be considered as studies report that 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

Perioperative anaphylaxis, which has a greater risk of death than other types 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 [NMBAs]) are the more common culprits. Rigorous evidence on this topic is lacking because of 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, if available) and/or in vitro-specific IgE testing should be performed to all potential pharmacologic and nonpharmacologic culprits used during the perioperative period, including alternatives for anesthesia at the health care facility. Published resources provide empirical, nonirritating 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 to 6 weeks after anaphylaxis is generally recommended because a "refractory period" may result in lack of skin testing response. Data reveal 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 nonpharmacologic agents associated with POA may be considered if equally efficacious, structurally unrelated alternatives 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 health care practitioners on the diagnosis and management of anaphylaxis. This updated practice parameter focuses on topics selected by the workgroup as described subsequently. By identifying knowledge gaps in the research literature, these guidelines may also help researchers to direct their 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 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. This document is intended to be used by allergy/immunology specialists and all health care providers who seek guidance on the evaluation and management of patients with anaphylaxis.

Evidence has evolved since the previous anaphylaxis practice parameters. 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 to 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 previously in the Resolving Conflicts of Interest section. Permission was obtained for all tables and figures for which it was required.

This practice parameter contains recommendations intended to optimize care of patients and to assist physicians and/or other health care practitioners and patients to make decisions regarding evaluation and management of suspected anaphylaxis. This practice parameter was not intended to be a document using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology, which was used for our previous focused anaphylaxis consensus-based guideline. 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. 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 recommendation and the certainty of the evidence for each CBS were determined by the group, based on their assessment of the anticipated benefits and harms, certainty (quality) of the evidence (including, when possible, magnitude of effect, indirectness, inconsistency, imprecision, and risk of bias), and contextual factors (resource allocation, costs, equity, feasibility, and acceptability). Although the consensus of the workgroup was not always unanimous, the recommendations reflect the majority opinion, and points of disagreement are clearly described in the text.

The strength of recommendation 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 1. 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 (eg, randomized controlled trials, observational studies, case series and reports) and factors that rate down or rate up the certainty of the evidence. The significance and implications of this rating are described in Table 2. 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 3 lists all the recommendations.

Main Text

Introduction and Background

Our understanding of anaphylaxis has grown steadily in recent years, but many important knowledge gaps remain.[1] 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.[2] 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.[2] 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 owing to chemotherapy infusions, aeroallergen rush immunotherapy, and RCM.[3] This 2023 Update is meant to complement the 2020 GRADE guideline, not to replace it or prior practice parameters.

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

Table 1
Grading the Strength of Recommendations[488]

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 the following:

- For patients—Most people in this 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 the following:

- For patients—Most people in this situation would want the recommended course of action, but many would not.
- For clinicians—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.

Abbreviation: JTFPP, Joint Task Force on Practice Parameters.

Table 2
Grading the Certainty of Evidence for Each Recommendation[489]

High = Large and robust randomized controlled trial(s) or systematic reviews and meta-analyses inform intervention effects. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate = The recommendation would likely be based on somewhat limited evidence, for example, randomized trials with study limitations. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low = The recommendation would likely be based on very weak evidence, for example, mostly observational studies (nonrandomized studies) and registries. 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.
Very low = The recommendation is based largely on very low quality studies and/or on expert opinion. Any estimate of effect is very uncertain.

Table 3
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). We suggest drawing a second tryptase measurement at a later time as a baseline for comparison to determine whether there was a significant acute elevation.	Conditional	Moderate
3	CBS	We suggest clinicians consider evaluation for HαT in patients with elevated bST level (8 ng/mL or greater).	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 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.	Conditional	Moderate
6	CBS	We suggest that meeting diagnostic criteria for anaphylaxis is not required before 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, because 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 does not correlate 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 on first exposure in infants.	Conditional	Low
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.	Conditional	Very low
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 childcare centers and schools implement staff training for allergy and anaphylaxis management.	Conditional	Very low
17	GRADE	We suggest that childcare 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 children who lack the capacity to self-manage.	Conditional	Very low
18	GRADE	We suggest that childcare centers and schools stock undesignated EAIs that can be used to treat any individual on school grounds who experiences anaphylaxis.	Conditional	Very low
19	CBS	We suggest clinicians counsel patients that although US regulations require disclosure of major allergens on labels of prepackaged foods, they do not require restaurants 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 (eg, jewelry or wallet card) be considered optional. If it is worn or carried, the wording on medical alert jewelry or wallet cards should be verified for accuracy by a health care professional.	Conditional	Very low
22	CBS	We suggest that keeping stock EAI in community settings be encouraged, if feasible.	Conditional	Very low
Epinephrine autoinjectors: when and how to prescribe				
23	CBS	We suggest 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.	Conditional	Very low
24	CBS	We suggest that in jurisdictions where single-packs of EAIs are available, clinicians consider a patient's risk factors for severe anaphylaxis, their values and preferences, and contextual factors when deciding whether to prescribe only 1 vs 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

(*continued*)

Table 3 (*Continued*)

Section and number	Method	Recommendation	Strength of recommendation	Certainty of evidence
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 not to give epinephrine preemptively 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 after epinephrine use if anaphylaxis is severe, fails to resolve promptly, fails to resolve completely or nearly completely, or returns or worsens after a first dose of epinephrine.	Conditional	Very low
27	CBS	Serious adverse reactions to intramuscular 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 adverse 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 patients may have experienced.	Strong	Low
Beta-blocker and angiotensin-converting enzyme inhibitor medications				
31	CBS	We suggest that patients with a history of insect sting anaphylaxis who are not receiving VIT may continue BB or ACEI medications 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 may be prescribed for patients with a history of insect sting anaphylaxis who are treated with BB or ACEI medication, with shared decision-making regarding the benefits and potential harms of concurrent VIT treatment and medication, compared with withholding either the treatment or the medication.	Conditional	Low
33	CBS	We suggest that, in most cases, treatment with BB or ACEI medication need 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 medication, with shared decision-making. It would be preferable to replace the BB or ACEI, if there is a safe and effective alternative.	Conditional	Low
35	CBS	We suggest that patients receiving maintenance dose AIT have a minimal increased risk of a severe anaphylactic reaction when on BB/ACEI medication and may consider continuing AIT and medications based on shared decision-making.	Conditional	Low
36	CBS	For planned procedures (eg, RCM, challenge/desensitization, and infusion), if the BB/ACEI medication 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 (eg, those with severe food allergy, mastocytosis or MCAS, or recurrent IA) be counseled about the risk of more severe anaphylaxis and consider avoiding, where possible, the use of nonselective BBs or ACEIs.	Conditional	Moderate
Mastocytosis and anaphylaxis				
38	CBS	We recommend clinicians 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 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.	Strong	Moderate
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 be continued indefinitely in patients with mastocytosis and insect sting anaphylaxis 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 be performed, when available, to all potential pharmacologic and nonpharmacologic culprits used during the perioperative period. If testing is not possible, we suggest referral to another center or, if necessary, use of the most efficacious agents structurally dissimilar from the most likely culprit.	Conditional	Very low
44	CBS	We suggest that immediate hypersensitivity testing to suspected culprit (and alternative) agents be delayed after POA, unless repeat surgery cannot be postponed. If surgery with general anesthesia is needed sooner, then testing may be performed when needed.	Conditional	Very low
45	CBS	We suggest that challenges be performed, when feasible, to all potential culprit agents to which skin and/or in vitro testing is negative, before or in conjunction with use of these agents for a future surgical procedure.	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

(*continued*)

Table 3 (*Continued*)

Section and number	Method	Recommendation	Strength of recommendation	Certainty of evidence
47	CBS	We suggest that avoidance of culprit pharmacologic and nonpharmacologic agents associated with POA may be considered, regardless of test results if challenge is not feasible and if equally efficacious, structurally unrelated alternatives are available.	Conditional	Low
48	CBS	We offer no recommendation for or against the use of pretreatment before return to the operating room in patients with negative cutaneous (percutaneous and intradermal) and/or in vitro-specific IgE testing (and challenge when possible) result to all suspected POA culprit agents.	None	Very low

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIT, allergen immunotherapy; BB, beta-blocker; bST, baseline serum tryptase; CBS, consensus-based statement; EAI, epinephrine autoinjector; EMS, emergency medical services; FAAN, Food Allergy and Anaphylaxis Network; HαT, hereditary α-tryptasemia; IA, idiopathic anaphylaxis; 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.

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.[2,3]

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.[4] Despite the advances in these areas, the body of evidence is still limited in relation to most questions and lacking for some. Clinically important questions must often be addressed indirectly through surrogate markers and outcomes, especially when there are low event rates, and the only published studies are observational and do not consistently report the same outcomes or use the same criteria.[3] These realities of anaphylaxis research lead to low or very low certainty of evidence, even when there are moderate-to-large numbers of patients studied. The goal of this workgroup was to identify the best available evidence of the past 7 years for the specific topics of interest and synthesize an expert assessment of the best clinical practices supported by this evidence.

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

Diagnosis of Anaphylaxis

Anaphylaxis is a systemic, usually multiorgan, potentially life-threatening syndrome. The diagnosis is clinical—there are no quintessential symptoms, findings, or laboratory markers. Through the years, the absence of a reference standard for diagnosis has challenged the ability to formulate a consistently accurate, universally accepted, evidence-based definition. Furthermore, the lack of a universal, standard, practical definition has contributed to both underdiagnosis and overdiagnosis, the former resulting in inadequate treatment, with possible increased morbidity and mortality, and the latter contributing to anxiety and unnecessary prescription of epinephrine.[5] 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 found in Box 1. There is also a need for improved equity and inclusivity in the evaluation and management of anaphylaxis. For example, increased mortality rate has been noted in minorities with anaphylaxis, particularly those of African American race, and outcomes in anaphylaxis are improved with use of an interpreter for shared decision-making, when indicated.[6]

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 respiration and/or the circulation, and it may occur without typical skin features, circulatory shock, or compromised breathing 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 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 and without re-exposure to an allergen trigger.
5. Biphasic anaphylaxis is unlikely when anaphylaxis is not severe and the patient remains symptom-free for one hour of 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 (e.g., 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 found in Table 4, the diagnosis of anaphylaxis over the years has varied with the country of origin, group or entity from which it was derived, and the intended application.[7–21] Although “multi-organ” has been part of many definitions from 2004 to 2016, a single-organ

Table 4
Anaphylaxis Definitions 2001 to 2021

Country, region, or organization	Date	Definition	Reference
EAACI	2001	Anaphylaxis is a severe, life-threatening, generalized or systemic hypersensitivity reaction	Johansson et al,[7] 2001
ASCIA	2004	Anaphylaxis is a rapidly evolving generalized multisystem 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,[8] 2006 and Brown et al,[9] 2006
USA/NIAID	2006	Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death (see Table 5 for NIAID anaphylaxis criteria)	Sampson et al,[10] 2006
Brighton Collaboration Working Group—International	2007	Anaphylaxis is an acute hypersensitivity reaction with multiorgan system involvement that can present as, or rapidly progress to, a severe life-threatening reaction. It may occur after 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,[11] 2007
US JTFPP 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,[12] 2010
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,[13] 2011
Pakistan	2013	Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death.	Khan et al,[14] 2013
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,[15] 2014
Germany	2016	Anaphylaxis is a severe, life-threatening, generalized or systemic hypersensitivity reaction. Grade 1: local with no systemic symptoms. Grade 2: mild/moderate systemic reaction with skin and/or GI. Grade 3: severe anaphylaxis, systemic with respiratory and/or cardiovascular involvement	Niggemann and Beyer,[16] 2016
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[21]
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.	World Health Organization 2021[17]
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,[18] 2019 and Cardona et al,[19] 2020
EAACI	2020	Anaphylaxis is a severe allergic reaction. [Defined in the context of when to use epinephrine autoinjectors]	Kraft et al,[20] 2020
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,[21] 2021
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 in a short period of time (within 1 hour of onset of the first symptoms or signs).	Gold et al,[24] 2022

Abbreviations: ASCIA, Australian Society of Clinical Immunology and Allergy; EAACI, European Academy Allergy and Clinical Immunology; GI, gastrointestinal; JTFPP, Joint Task Force on Practice Parameters; NIAID, National Institute of Allergy and Infectious Disease; PP, practice parameter; WAO, World Allergy Organization; WHO, World Health Organization.

system may exhibit major involvement with more physiological 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.[22] Laryngeal, respiratory, and/or cardiovascular involvement is common in fatal anaphylaxis.[23]

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 consisted of 2 sentences.[18,19] The first is similar to the 2006 NIAID definition but with "systemic hypersensitivity" substituted for "allergic" to be more precise (Table 4).

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 and clinical diagnostic criteria[10] (Table 5). These criteria have been widely adopted[25] and were found to be 95% sensitive and 71% specific in a prospective validation study among emergency department (ED) patients.[26] Knowledge deficits regarding anaphylaxis recognition and treatment continue to be revealed.[27,28] In an effort to simplify anaphylaxis diagnostic criteria, in 2019 the WAO Anaphylaxis Committee proposed revisions to the definition for the clinical diagnostic criteria for anaphylaxis, which was subsequently largely adopted by the WAO 2020 guidance (Table 5).[18,19]

With regard to the 2020 WAO criteria, although most cases of anaphylaxis are likely to be categorized the same as the 2006 NIAID criteria, there are several notable differences, mostly related to the timing, the associated exposures, or the specific organ systems involved. Some examples are listed here and found in Table 6.

1. Although the 2006 NIAID criteria include cases of isolated hypotension, but not isolated respiratory reaction, after exposure to a known allergen, the 2020 WAO criteria would include reactions with acute-onset hypotension, including those with bronchospasm or laryngeal involvement (eg, stridor, vocal changes, or odynophagia) after exposure to a known or highly probable allergen in the absence of typical skin involvement. These criteria exclude respiratory compromise triggered by common inhalant allergens.

Table 5
NIAID and WAO Side-by-Side Comparison[10,19]

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) 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	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.

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

2. Although both the 2006 NIAID and 2020 WAO criteria note that symptom onset would be expected within "minutes to several hours," the 2019 WAO anaphylaxis committee guidance, which informed the WAO 2020 criteria, also 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.[18]
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.[18] 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.[19]
5. Finally, to simplify the definition, the 2020 WAO criteria essentially combine the first and second (of 3) 2006 NIAID criteria, creating a definition with only 2 criteria. Therefore, with the 2020 WAO definition, all anaphylaxis cases must have mucocutaneous symptoms except those that meet the second 2020 WAO criterion (Table 5). 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 owing 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" (eg, childhood viral gastroenteritis with acute urticaria) would meet the 2020 WAO criteria but not the original 2006 NIAID criteria.

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,

Table 6
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,[b] or laryngeal involvement[c]
Respiratory	GI	Only if likely allergen exposure	Only if known or highly probable allergen with bronchospasm[b] or laryngeal involvement[c]
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[c]	None	No	Only if highly probable allergen exposure
Bronchospasm[b]	None	No	Only if highly probable allergen exposure

Abbreviations: BP, blood pressure; CV, cardiovascular; GI, gastrointestinal; NIAID, National Institute of Allergy and Infectious Disease; WAO, World Allergy Organization.
NOTE. 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 (1) Infants and children under 10 years: systolic BP less than (70 mm Hg + [2 × age in years]). (2) Adults and children above 10 years: systolic BP less than 90 mm Hg.
[b]Excluding lower respiratory symptoms triggered by common inhalant allergens or food allergens perceived to cause "inhalational" reactions in the absence of ingestion.
[c]Laryngeal symptoms include stridor, vocal changes, and odynophagia.

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 previously.

Although 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 after an immunization was proposed by the Brighton Collaboration Anaphylaxis Working Group in 2007.[11] The case definition included sudden onset, rapid progression, and multiple-organ system involvement (Table 7). Diagnostic levels of certainty were based on fulfilling major and minor criteria consisting of signs and symptoms and tryptase level 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 the cases.[29] 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.[19,29] Thus, a patient with lip swelling and itchy eyes would meet the case definition of anaphylaxis with level 2 diagnostic certainty, potentially leading to overdiagnosis of anaphylaxis in the setting of immunizations.[30] Application of the 2006 NIAID or 2020 WAO criteria may be more accurate, but further studies are needed (Table 5).[31,32] As a result of increased use during the COVID-19 pandemic, and debate regarding the Brighton Criteria performance in assessing vaccine-associated anaphylaxis compared with NIAID or WAO criteria, the Brighton Collaboration Anaphylaxis Working Group published an updated and revised version 2 of the criteria in late 2022 (Table 7). The revised criteria focus the major and minor criteria on the reporting of observable clinical signs, rather than subjective symptoms, and provide a clearer approach to the ascertainment of levels of certainty.[24] These modified 2022 Brighton Criteria may be more consistent with other common case definitions for anaphylaxis.

The course of anaphylaxis can be variable across patients and populations, although one study has reported some consistency among recurrent anaphylaxis for individual patients.[33] For most patients, anaphylaxis is not persistent, refractory, or biphasic[34–37]; however, these subtypes of anaphylaxis are not uncommon.[34–45] 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.[3] 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.[3,46,47] Persistent, refractory, and biphasic anaphylaxis may be defined by clinical criteria (Table 8). *Persistent anaphylaxis* is highly likely when anaphylaxis persists for at least 4 hours.[34] *Refractory anaphylaxis* is highly likely when anaphylaxis continues despite appropriate epinephrine dosing and symptom-directed medical management (eg, intravenous fluid bolus for hypotension).[34] Data from the European Anaphylaxis Registry suggest that refractory anaphylaxis accounts for less than 0.5% of severe anaphylaxis cases, with an associated drug etiology (particularly in the perioperative/procedural setting) most frequently recognized.[48] Refractory anaphylaxis increases the risk for anaphylaxis fatality (26.2% vs 0.35% in a 2019 European registry, $P < .0001$).[48,49] *Biphasic anaphylaxis* is highly likely when the patient develops anaphylaxis after initial signs and symptoms have completely resolved for at least 1 hour before the onset of repeated anaphylaxis within 48 hours without re-exposure to an allergen trigger.[34] In a meta-analysis that included 2890 adult patients with anaphylaxis, the median percentage of patients with biphasic anaphylaxis was 6.5% (range, 0.4%-20%).[40] The median duration between resolution of the initial episode and the secondary reaction was 10.5 hours (range, 1.75 hours-17 hours).[40] These findings are in range with other studies of biphasic anaphylaxis.[3,43,44,50] Notably, a 1-hour symptom-free observation after resolution of initial anaphylaxis was associated with a 95% negative predictive value (95% CI, 90.9%-97.3%) for biphasic anaphylaxis.[40] Persistent anaphylaxis is distinct from biphasic anaphylaxis because in persistent anaphylaxis there is no period of resolution between an initial and a subsequent phase.[34] In 1 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.[35] Fatal anaphylaxis is a rare outcome.[51,52] In a population-based epidemiologic study using 3 national databases, the case fatality rate among patients hospitalized or with ED presentations was between 0.25% and 0.33%.[53]

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.[3,54–56] 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) and the patient (eg, immune response, behaviors, concomitant medications, and other patient-specific factors and comorbidities) (Fig 1).[57–60] Patients with severe anaphylaxis are more likely to have hypotension and hypoxemia, and severe anaphylaxis is associated with older age, preexisting lung disease, and drug etiology.[22] Nevertheless, anaphylaxis is part of a spectrum of acute allergic reactions that range from mild to fatal.[18,61,62] 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.[57] Any definition of anaphylaxis severity must clearly inform all stakeholders.

Multiple severity grading systems have been developed,[16,57,63–65] and the term "severity" can have different meanings to patients, clinicians, and investigators.[57,63] In 1977, Ring and Messmer[66] proposed a 4-category classification system to describe severity of reactions to colloid volume substitutes, but this system was not specific to anaphylaxis. The Ring and Messmer classification was subsequently modified such that grade I represents isolated mucocutaneous involvement, grade II mild-to-moderate severity multiorgan system involvement, grade III life-threatening symptoms in a single-organ system or more severe multiple-organ system involvement, and grade IV cardiac or respiratory arrest.[67,68] Additional grading schemes have been proposed through the years. An approach involving 5 categories proposed by Sampson for grading of food-induced anaphylaxis was subsequently adopted by the EAACI in 2007.[69,70] In 2004, Brown[63] proposed a simple classification system for the range of hypersensitivity reactions, with mild reactions limited to cutaneous manifestations; moderate reactions characterized by features suggesting respiratory, cardiovascular, or gastrointestinal involvement; and the most severe grades characterized by hypoxia, hypotension, and/or neurologic compromise (Table 9). Many clinicians continue to use the 2010 WAO Subcutaneous Immunotherapy Systemic Allergic Reaction Grading System,[71] often applying modifications based on age and allergen trigger.[19,65,72] 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.[73] In addition, the Food Allergy Severity Score was recently developed using the EuroPrevail outpatient clinical cohort of 8232 food allergy reactions.[74]

There are limitations to existing anaphylaxis severity scoring systems. For example, the Brown severity grading system, developed

Table 7
Case Definitions and Differences Between the 2007 (Version 1) and 2022 (Version 2) Brighton Collaboration Anaphylaxis Major and Minor Criteria[24]

	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 replaced with *acutely* in BC-V2; a clearer description of *rapid progression* has been provided; and multisystem 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. Urticaria 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 urticaria, 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: tachypnea, increased use of accessory respiratory muscles (sternocleidomastoid, intercostal), recession, cyanosis, grunting	Expiratory wheeze documented by health care professional which could be with/out stethoscope; inspiratory stridor documented by health care 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 health care professional—this does not include isolated lip swelling; 2 indicators of respiratory distress: tachypnea, cyanosis, measured hypoxia with oxygen saturations < 90%, grunting, chest wall retractions, increased use of accessory respiratory muscles	Inclusion of wheeze, stridor, upper airway swelling documented by a health care professional. Removal of lip swelling as a sign of upper airway angioedema. Inclusion of measured hypoxia with oxygen saturations <90%.
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 that 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 × baseline tryptase) + 2 ng/mL.
Minor laboratory	Elevated mast cell tryptase	None	
Level of certainty			
Level 1	≥1 major dermatologic 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	

(*continued*)

Table 7 (*Continued*)

	Brighton collaboration criteria version 1 (2007)	Brighton collaboration criteria version 2 (2022)	Comments
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.	

Table 8
Clinical Criteria for Diagnosing Persistent, Refractory, and Biphasic Anaphylaxis

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 h.
Refractory anaphylaxis is highly likely when both of the following 2 criteria are fulfilled: 1. Presence of anaphylaxis after 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 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 h from complete resolution of the initial symptoms or examination findings.

NOTE. Adapted from Dribin et al.[34]

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 physiological measurements (eg, blood pressure and oxygen saturation).[63] Grade 1 would not be considered anaphylaxis, whereas 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.[63] 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 after exposure to a suspected allergen. In an analysis of 259 food-induced anaphylaxis episodes from 157 children, a 24.7% to 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.[75]

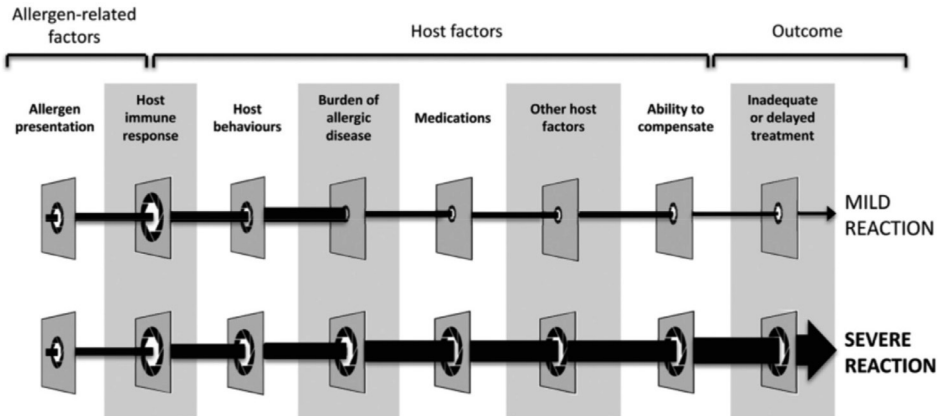

Figure 1. Risk factors for severe allergic reactions. Many factors may modulate between mild and severe allergic reactions.
Adapted with permission from Dubois et al[60] and Smith et al.[59]

Table 9
2004 Brown Grading System for Hypersensitivity Reactions

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 ≤ 92%, hypotension (systolic blood pressure <90 mm Hg in adults), confusion, collapse, altered level of consciousness, or incontinence.

NOTE. Adapted from Brown, 2004.[63]

In 2021, a severity grading system for allergic reactions proposed by Dribin et al[61] resulted from an expert consensus and synthesis of the many prior grading scales with additional granularity but also added some degree of complexity (Fig 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 it will likely require the use of decision support tools or memory aids to be most effective. Although 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[76] evaluated 10 severity grading systems, concluding that geographic location of the health care provider may affect severity assessment and that all scoring systems have limitations in discriminating anaphylaxis severity.

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). We suggest drawing a second tryptase measurement at a later time as a

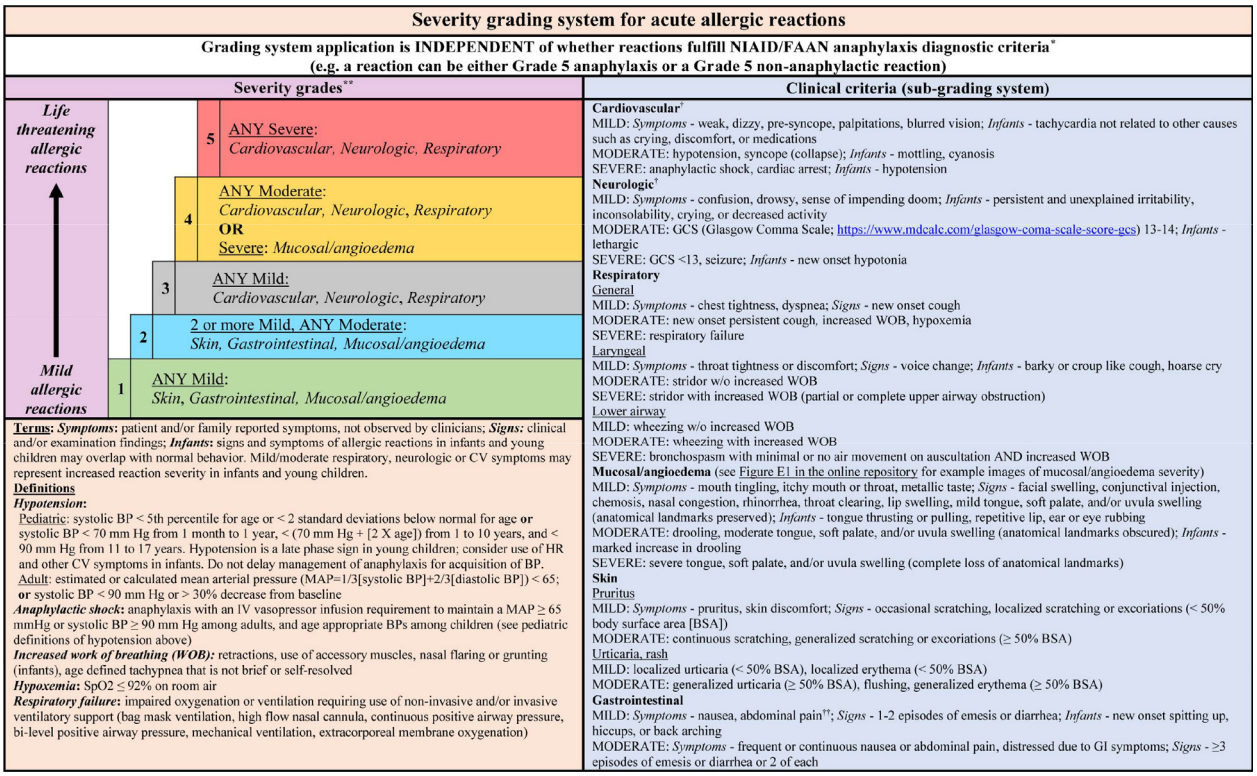

Figure 2. Anaphylaxis consensus severity grading system. BP, blood pressure; CV, cerebrovascular; FAAN, Food Allergy and Anaphylaxis Network; GI, gastrointestinal; HR, heart rate; MAP, mean arterial pressure; NIAID, National Institute of Allergy and Infectious Diseases; SpO_2, oxygen saturation.

Reproduced with permission from Dribin et al 2021.[61]

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 neurologic involvement may have urinary or stool incontinence. However, the significance of incontinence as an isolated symptom is unclear, and it is therefore not included as a symptom in the subgrading system.

†† Abdominal pain may also result from uterine cramping.

baseline for comparison to determine whether there was a significant acute elevation.

Strength of Recommendation: Conditional

Certainty of Evidence: Moderate

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

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 workup for patients presenting with suspected or presumed anaphylaxis is broad (Table 10, Fig 3).[2] Diagnostic workup relies on a thorough clinical history with attention to patient age, sex, medical and atopic history, concurrent medications, 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 evaluate for IgE-mediated triggers (eg, skin and/or serum testing).[2] As part of the diagnostic evaluation, it is imperative to confirm that the events in question are indeed anaphylaxis, classically by finding objective signs of mast cell activation on physical examination (eg, urticaria, wheezing on lung auscultation, or hypotension) or by elevated tryptase level to rule out mimickers of anaphylaxis (Table 10).[77,78] One must realize that when evaluating for an elevated acute tryptase level, a serum tryptase level above the laboratory-defined normal value (eg, >11.4 ng/mL in many laboratory results) 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 that 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.[79,80] Although this equation was proposed to aid in diagnosis of MCAS rather than anaphylaxis, it has been validated in POA in 1 study, suggesting a specificity of 91% and sensitivity of 78% (in this cohort, the positive and negative predictive values were 98% and 44%, respectively).[77] Questions remain regarding the overall utility of using this equation for anaphylaxis in general (eg, what is the normal temporal intrapersonal variance in tryptase and what is the value in food-induced anaphylaxis).[78] For example, Mateja et al[80] revealed 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 cutoff values could be tailored to the index of clinical suspicion,[80] suggesting a cutoff 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.[81] Thus, currently, we do not recommend using the 20% plus 2 ng/mL equation alone to diagnose anaphylaxis.

Since publication of the 2015 anaphylaxis parameter, there are 2 updated considerations for evaluating patients with recurrent mast cell-mediated symptoms/recurrent IA. The first is examination not only for elevated bST level (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 level (usually >8 ng/mL).[82,83] 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.[84,85] Incorporating copy number can be useful in determining whether further evaluation of a clonal mast cell evaluation may be warranted (https://bst-calculater.niaid.nih.gov).[86] HαT occurs in 5% to 7% of people in the European and North American populations sampled,[87] and although many individuals with HαT are asymptomatic, there are data to suggest that it is often accompanied by a wide range of symptoms consistent with mast cell mediator release.[88] However, in a random biorepository population, there was no difference in the clinical symptomatology or medical history of individuals with HαT compared with controls.[89] 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.[90,91] Our understanding of HαT is incomplete, and at this point, the degree to which the diagnosis alters management is uncertain.[85,92] Still, HαT should be considered in the differential diagnosis of patients with elevated bST level 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 the Spanish Mastocytosis Network (referred to as the REMA score) and described patients with severe systemic symptoms of mast cell mediator release but without cutaneous lesions, including many patients with insect venom anaphylaxis (Fig 4).[93] A more recent study in the United States describes the NICAS (NIH Idiopathic

Table 10
Anaphylaxis Differential Diagnosis

Anaphylaxis
- Anaphylaxis due to known allergens—for example, foods, drugs, insect sting, latex
- Anaphylaxis associated with physical stimuli—for example, exercise, cold, heat
- Anaphylaxis associated with both—for example, food-dependent exercise induced
- Idiopathic

Mastocytosis and mast cell activation syndromes, hereditary α-tryptasemia

Vasodepressor reactions
- Vasovagal

Flushing syndromes
- Neuroendocrine tumors, for example, carcinoid, pheochromocytoma
- Vasoactive intestinal peptide-secreting tumor

Restaurant syndromes
- Scombroidosis
- Monosodium glutamate

Nonorganic 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
- Vancomycin infusion reaction ("red man syndrome")
- Autonomic dysfunction

NOTE. Adapted from Lieberman et al.[2]

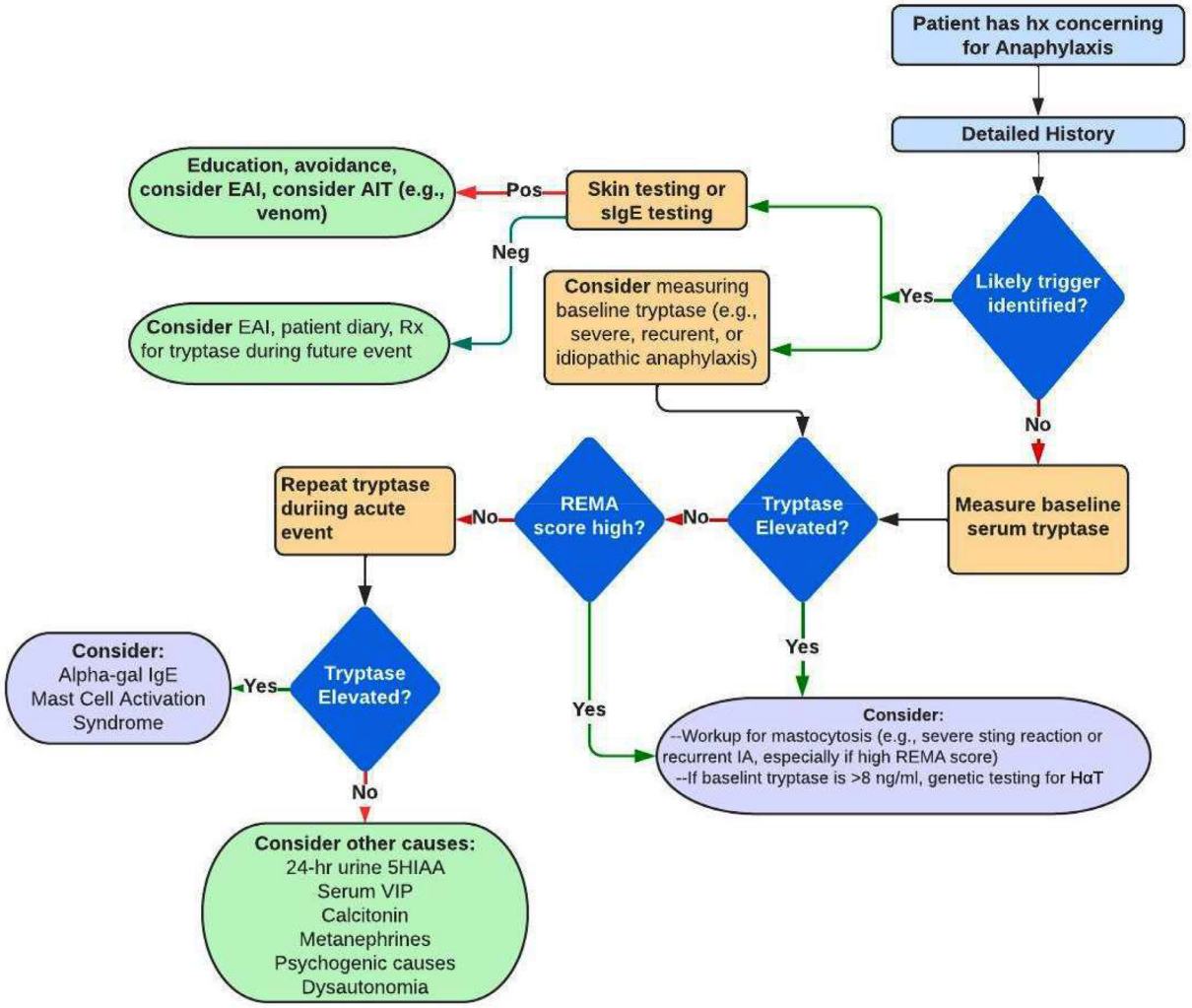

Figure 3. Diagnostic evaluation of the patient with a history of anaphylaxis.

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.

Clonal Anaphylaxis Score) score in patients with IA (none had venom anaphylaxis; Fig 4).[94] In this study, 14% of patients with IA were diagnosed with having 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 have a negative result,[95] within the NICAS score the predictive value may improve. The REMA score has been validated and modified in other studies.[96,97] 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.[93,94,96,98] However, bone marrow biopsy may be considered in patients with recurrent or severe anaphylaxis episodes outside of these scoring systems.

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 geographic location.[99,100] As with other allergies, alpha-gal asymptomatic sensitization occurs and does not always equate to clinically reactivity. Clinical history (anaphylaxis occurring hours after consumption of red meat), geographic 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 United States[101] and Germany[102] were found to have 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 with 26 healthy controls, with a positive predictive value and negative predictive value of 92% and 83%, respectively, at a value of greater than 1.0 kU/L in this sample (although these predictive values may not be generalizable in other populations).[103] Thus, when ordering the alpha-gal sIgE, the clinician should use the history

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

Figure 4. Scoring systems to evaluate risk of a clonal mast cell disorder in anaphylaxis. NICAS, NIH Idiopathic Clonal Anaphylaxis Score; REMA, Red Espanola MAstocitosis Reproduced with permission from Lieberman et al[98] and Carter et al.[94] Adapted from Alvarez-Twose et al.[93]

to assess the pretest 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 result 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 before 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 health care settings[27,104–114]; however, evidence suggests more appropriate use in locations with systems designed for recognition and treatment.[105,115] Although all cases of anaphylaxis represent a systemic hypersensitivity reaction, not all systemic hypersensitivity reactions fulfill diagnostic criteria for anaphylaxis (eg, generalized urticaria without additional symptoms after any form of AIT).[75] 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 (eg, hypotension or respiratory distress) to distinguish anaphylaxis from non-anaphylactic systemic hypersensitivity reactions at any point in time.[10,19]

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 epidemiologic 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. Although the NIAID/FAAN criteria are often used in clinical practice, their diagnostic precision is imperfect.[116]

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.[61,117] Thus, meeting anaphylaxis diagnostic criteria is not requisite before epinephrine use in treating a systemic hypersensitivity reaction.[27] 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.[28] Early epinephrine

Table 11
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.

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

treatment of a systemic hypersensitivity reaction may be more effective than delayed treatment.[118,119] 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).[3] However, epinephrine use in patients before 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.[120–122] Notably, appropriate use of epinephrine during anaphylaxis improves quality of life and self-efficacy.[123] 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 before the development of hypotension.[124] 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.[125–127] 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).[128,129]

A recent expert consensus of knowledge gaps in anaphylaxis was published.[4] Further research efforts are expected to continue to inform knowledge gaps in the area of anaphylaxis diagnosis. These are summarized in Table 11.

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 agree that food is clearly the most common cause of anaphylaxis in this age group and that this is consistent across the globe.[130–134] In addition, the rate of presentation to the ED for anaphylaxis in this age groups seems to be increasing (at least in the United States).[130]

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

Recommendation 8 (CBS): We suggest that clinicians use current NIAID/FAAN or WAO anaphylaxis criteria to assist in the diagnosis of anaphylaxis in infants/toddlers, because 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.[10,19] 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.[135] 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 the following: 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 nonverbal or minimally verbal populations; establishing appropriate epinephrine dosing for infants and toddlers; and lack of a standardized evaluation for patients of this age.[135]

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 does not correlate 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 on first exposure in infants.

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 Nationwide Emergency Department Sample (a large, national study of temporal trends of presentation to US EDs from 2006 to 2015) noted that the proportion of visits for anaphylaxis in infants increased from approximately 20 to 50 per 100,000 visits through this time period, whereas overall hospitalizations for anaphylaxis presenting to the ED in this age range fell from 19% to 6%.[136] 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 Healthcare Cost and Utilization Project Nationwide Inpatient Sample reveal that general admission rates were stable in infants and toddlers during that same time frame.[137] 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 have largely noted that anaphylaxis is an uncommon manifestation of initial reactions, and overall, although severe reactions occur, they are far less common than mild-to-moderate, primarily cutaneous, reactions.[138–144] Data from an Australian

Table 12
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 with 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 whether needle length of available 0.1 mg and 0.15 mg autoinjectors provides more optimal intramuscular delivery of epinephrine.
Lack of data to determine whether potentially higher doses (eg, >0.01 mg/kg) of epinephrine delivered using a 0.15 mg autoinjector in an infant <10 kg lead 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 health care utilization.

population-based, cross-sectional study of 12-month-old infants revealed that fewer than 2.5% of all reactions after initial introduction of the food were severe.[145] A national Korean ED registry which revealed that 9.7% of children aged below 24 months (n = 93 children of 558 total participants) who presented with anaphylaxis had what was considered by investigators to be a severe reaction.[146] 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.[147–149] Retrospective studies report that infants and young children more often have skin symptoms as compared with older children whereas infants less often have respiratory symptoms.[147,148] 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 aged below 12 months as compared with older toddlers.[150] In infants, behavioral manifestations may include unexplained behavioral changes, such as withdrawal, inconsolable crying, irritability, or clinging.[135,150,151] 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 to 15 kg where formerly only 0.15 mg and 0.3 mg doses were offered.[135] 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.[2] 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.[2] Data have emerged regarding the importance of needle length in smaller infants or toddlers. Ultrasound-based evaluations of skin-to-bone distance suggest that longer needles increase the risk of the needle hitting bone. This could lead to impaired delivery of the epinephrine, increased pain and distress, or needle embedment in bone requiring surgical extraction.[153,154] We found only 1 case report of intraosseous injection of the femur, which occurred when an EpiPen Jr. was administered to a female child weighing 25 kg.[155] More research is needed to determine the true risk of intraosseous injection and how it may affect the efficacy of epinephrine if it occurs.

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 12, with recommendations to help guide future research.

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. Although there are abundant data addressing the frequency and management of anaphylaxis owing to different allergen triggers, there are little data regarding the frequency of anaphylaxis in specific community locations or on effec-

Table 13
Frequency of Anaphylaxis in Different Locations[a]

Population studied		Home	School/work	Restaurant	Other home
Children	Studies, n	44	46	26	16
	Average[b]	57%	11%	8%	14%
	Range	37%-92%	0%-28%	0%-17%	3%-34%
Adults	Studies, n	4	3	3	
	Average[b]	42%	3%	22%	
	Range	27%-60%	2%-5%	17%-33%	
Age not specified[c]	Studies, n	8	8	7	
	Average[b]	46%	9%	21%	
	Range	16%-68%	4%-21%	6%-51%	

Average = average frequency of anaphylaxis across the number of studies.[b]
Range = range across the number of studies (wide range across the locations).
References for child.[132,161–201,207]
References for all ages.[132,190,199,202–206]
References for adults.[197–199]
[a]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 takeout 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.
[b]Unweighted average may be misleading; note the range of averages across studies.
[c]When studies report the location of anaphylaxis for "all age groups," the authors usually fail to report the location by age category.

tive mitigation strategies by location. Despite the low quality of available evidence, the workgroup has judged that the desirable effects of certain interventions clearly outweigh the undesirable effects. Thus, we have issued strong consensus-based statements based on very low- to moderate-quality evidence, similar to good practice statements under the GRADE methodology.

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 may 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, including missing information. Table 13 presents the calculated percentage range and the average frequency of anaphylaxis in children and/or adults by reported location.[132,161–207] The younger the population, the higher the percentage of anaphylaxis events occurring in the "home" location.[192] A study in which 89% of 5149 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.[205] Although fatalities have been reported, they are rare.[190] 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.[190]

Anaphylaxis in Childcare Centers and Schools

The JTFPP endorses the following GRADE recommendations from 2021 guidelines for the management of allergic reactions in childcare centers and schools.[208]

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

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

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

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

Recommendation 17 (GRADE): We suggest that childcare 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 children who lack the capacity to self-manage.

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

Question: Should childcare centers and schools stock undesignated EAIs that can be used to treat any individual on school grounds who experiences anaphylaxis?

Recommendation 18 (GRADE): We suggest that childcare 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 childcare centers and schools found that approximately 1 in 10 allergic reactions and cases of anaphylaxis in children occur in childcare centers or schools.[208] Across studies, the median reported rate of anaphylaxis in childcare centers or schools was 19 per 100,000 students per year (range: 8-118/100,000).[208] The GRADE guideline conditionally recommended that childcare 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 children at risk of

anaphylaxis. Staff training is linked to short-term improvements in allergy-related knowledge, skills, and preparedness among childcare and school personnel.[208] 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.[174,208–214]

Studies have not consistently found that food bans improve quality of life[215] or lower the risk of allergic reactions among students.[171,172,216] Thus, the GRADE guideline conditionally recommends that childcare centers and schools not implement site-wide food prohibitions (eg, "nut-free schools"). The guideline also conditionally recommends against classroom-level food 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.[208]

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 childcare 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 (eg, parties, crafts, science projects) or field trips.

The 2021 GRADE guidelines also conditionally recommended that childcare 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.[208] 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 treatment of individuals with no known history of allergy (15%-31% of reported cases of epinephrine use at childcare centers and schools are for those with no known allergy).[208] At this time, not all states have laws that require schools to have stock epinephrine available.[217]

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, they do not require restaurants 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 evaluated 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 few staff receive specific training.[218–220] 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 used 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[221] 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 United States have enacted laws related to food allergy awareness and/or signage, but these are not universal. A few restaurants list allergens or ingredients on their menu or other signage, a practice that seems to be increasingly adopted.[218] 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 labeling.

Researchers have used data from a national voluntary online registry to characterize food-allergic reactions in restaurants.[222] Cafes, fast food establishments, and Asian restaurants (as described by the authors) 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. More than 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 takeout foods.[223] In an online survey of parents of children with food allergy ordering takeout, the most common allergens triggering reactions were milk, peanut, and wheat, which often seemed as "hidden allergens" (eg, unlabeled, inapparent, or contaminant components). Takeout 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 takeout diners who experienced reactions was no less than by those who did not have reactions. An AAAAI workgroup on food allergy in restaurants has provided guidance for practitioners, patients, and restaurant staff.[224]

Table 14 presents potential strategies for safe dining to be considered when counseling patients who have food allergy. Management of anaphylaxis risk is a "shared responsibility" in the restaurant setting (ie, 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.

Currently, there are no US mandates for restaurants to have medical emergency kits with epinephrine on site. However, most states have passed legislation that allows restaurants to keep stock epinephrine on site.[225] 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.[226]

Anaphylaxis Inflight

An allergic inflight emergency is estimated to occur once for every 37,750 flights and for less than or equal to 1 of 2 million passengers, with emergency landings reported for less than 4.4% of these episodes. When patients with peanut and/or tree nut allergy have been surveyed, 1.7% to 10.7% reported having experienced an allergic reaction while on a commercial flight.[227–229] 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% to

Table 14
Potential Expert Opinion-Based Strategies and Considerations for Safe Dining to Discuss With Patients Who Have Food Allergy

	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 by speaking to the restaurant or checking online resources.
2.	Disclose allergy to a knowledgeable and responsible food service staff member before 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, before 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, for example, 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 (eg, 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 (eg, foreign travel), consider providing a translation of this list.	Allergy cards (eg, 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 traveling or if there is a language difference between the diner and 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 diner with allergy.
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 is 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 (eg, patient's purse) and provide instructions on how to use it.
6.	Be aware that there is likely higher risk of exposure to certain allergens at certain venues, including: peanut, and/or tree nut exposure in Asian restaurants; exposure to peanut, tree nuts, and/or milk in bakeries and ice cream shops; and seafood at restaurants that predominantly serve seafood. Practice extra vigilance or possibly avoid such 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 frequently serve their allergens because 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 whether 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, and so on.
8.	Only eat food prepared specifically for the diner with allergy 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.

Abbreviation: EAI, epinephrine autoinjector.

15% of cases across studies,[227–230] although reports of symptoms suggested that epinephrine might have been indicated in more cases.[228,230] Food allergens are the primary trigger for inflight reactions, with peanut implicated most frequently as the culprit food.[227–230] It is possible that there is underreporting of inflight reactions given past data that 29% to 50% of reactors notified airline personnel of their reactions.[227–229]

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.[231] A 2013 international study of inflight reaction found that certain reported risk mitigation strategies were associated with lower odds of reporting an inflight allergic reaction.[229] However, no prospective studies have evaluated whether implementation of these strategies lowers the risk of anaphylaxis. Although airline pre-notification is often suggested, it can potentially result in unintended consequences. 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.[232] Many airline websites provide some information for patients with allergy; however, only a few offer allergen-free meals for preorder or allow priority boarding.[233]

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,[234] half of venom anaphylaxis cases occurred in gardens and parks, 25% in public places or at work, and 25% in an unspecified location. On the basis of patient questionnaires, insect sting anaphylaxis occurs in 0.34% to 8.9% of the general population,[235,236] accounts for 1.5% to 50% of ED visits for anaphylaxis,[51,235] and is responsible for 13% to 33% of all fatal cases of anaphylaxis.[51] Measures for minimizing chances of insect stings have been suggested in the 2016 stinging insect hypersensitivity practice parameters.[237]

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 are 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 nonsteroidal anti-inflammatory drugs is most common, and most reactions occurring outside the medical setting are likely to occur in the home.

Table 15
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

Abbreviation: EAI, epinephrine autoinjector.

Question: Should clinicians advise use of medical identification (eg, 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 (eg, jewelry or wallet card) be considered optional. If it is worn or carried, the wording on medical alert jewelry or wallet cards should be verified for accuracy by a health care 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 and not standardized, and there is no requirement for physician verification of accuracy.[238,239] It is unknown whether medical alert jewelry or wallet cards reduce the risk of anaphylaxis or result 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 EAI in community settings be encouraged, if feasible.

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

Studies reveal that in the United States, sports facilities, airports, and amusement areas are the most common places where automated external defibrillators are used.[240,241] Therefore, some people suggest that these same locations should, ideally, have undesignated EAIs available.[242] All states have passed legislation that permits (but does not require) "entities" to stock undesignated epinephrine for emergency use.[225,243] "Entities" vary by state and may include camps, theme parks, sports arenas, restaurants, childcare centers, and/or college campuses, and this legislation is often separate from a state's school-entity stock epinephrine legislation. 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.[234,244] Availability of stock EAI on airplanes has been found to be cost-effective and may be a safer option than stock ampules and syringes in this setting.[245,246]

Knowledge gaps related to anaphylaxis in community settings are listed in Table 15. The key points reviewed in this section are summarized in Table 16.

Epinephrine Autoinjectors: When and What to Prescribe

Epinephrine is universally recommended as the first-line treatment for anaphylaxis.[3] However, the rate of EAI prescription for patients at risk of anaphylaxis remains suboptimal.[111,247] Even when clinicians prescribe EAIs, patients do not always adhere to their treatment plans, with researchers reporting suboptimal rates of EAI prescription fills and refills, carriage, and use.[111,247,248] 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 suggest 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, but the pattern and sequence of symptoms are more reproducible.[33] 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), the ease with which they may avoid causative agents or circumstances, and 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.[249,250] 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, likelihood of allergen exposure, and other potential cofactors that could affect the likelihood of a poor outcome.

For patients with food allergy, even small amounts of causative allergen may potentially trigger an allergic reaction—including anaphylaxis in some cases. Owing 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.[251] These are most frequently reported during the dose escalation when treatment

Table 16
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.
Childcare centers and schools	• Implementation of training programs for childcare 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 (and their families) to always have them available at their childcare 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 (eg, bring own safe food when traveling, read ingredient labels). • Although airplane emergency kits in the United States contain epinephrine (both 1:1000 w/v [1 mg/mL] and 1:10,000 w/v [0.1 mg/mL]), drawing up appropriate doses using a needle and syringe in a cramped air cabin midflight 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, insects, and 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.

Abbreviation: EAI, epinephrine autoinjector.

is initiated and during subsequent buildup dosing; however, home maintenance doses can also be associated with severe reactions, even with doses previously tolerated.[252] In a recent systematic review and meta-analysis, high-certainty evidence revealed 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 (risk ratio = 2.7) compared with avoidance or placebo.[253] 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 honey bee VIT and fire ant whole body extract immunotherapy offer less complete protection.[237]

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 health care settings, where health care professionals are equipped to administer epinephrine.[254] However, in up to 1 in 10 cases of drug- or RCM-induced anaphylaxis, the patient experiences a biphasic reaction, which is likely to occur outside of the health care setting.[37,255] The JTFPP found that the greatest risk factor for biphasic reaction is an initial presentation that requires multiple epinephrine doses to treat anaphylaxis (odds ratio [OR] = 4.82; 95% CI, 2.70-8.58).[3]

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.[256] Many of the reactions were reported to occur more than 2 hours after injection or after a number of uneventful doses. In 2007, this led the AAAAI and ACAAI's Omalizumab Joint Task Force to recommend the prescription of EAIs to patients prescribed omalizumab.[257] In a subsequent 2011 review, the Omalizumab Joint Task Force found that omalizumab-induced anaphylaxis most often occurred within the first 3 injections and within 2 hours after injection.[258] Another review found that 64% of the 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.[259] More recently, a retrospective study of 91 patients with difficult-to-control asthma found that of 10,472 injections of omalizumab, no anaphylaxis occurred.[260] In another study, 0.17% (n = 6) of 3620 adult patients with severe asthma experienced omalizumab-induced anaphylaxis in a treatment course of 52 months.[261] 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 fourth dose onward if determined appropriate 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. Nevertheless, a cost-effectiveness analysis revealed that for many patients, home injection of omalizumab is a cost-effective strategy.[262]

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.[263–265] 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. Although most 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.[266] Severe

Table 17
Likelihood of Requiring Treatment With Prescribed EAI

Allergic condition	Lower likelihood	Higher likelihood
IgE-mediated food allergy		• History of prior systemic allergic reaction after 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 y 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 • Honey bee allergy • Elevated basal tryptase level • Frequent exposure
Latex allergy	• Low likelihood of exposure	• Occupational exposure
Drug allergy	• Low likelihood of exposure	• Occupational exposure (eg, compounding, mixing, or preparation of medications)
Exercise-induced anaphylaxis		• All cases
Physical urticarias		• Cold induced
Aeroallergen immunotherapy	• No history of prior systemic reaction(s) to AIT and no relevant comorbidities (eg, asthma)	• History of prior systemic reaction(s) to AIT and/or relevant comorbidities (eg, asthma)

Abbreviations: AIT, aeroallergen immunotherapy; EAI, epinephrine autoinjector; VIT, venom immunotherapy.

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. More research is needed to evaluate the safety and efficacy of SLIT for food allergy, but studies to date suggest that adverse events are typically limited to local oropharyngeal or gastrointestinal symptoms, and systemic reactions requiring treatment with epinephrine are rare.[267] 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 owing to any cause, prior systemic reactions to immunotherapy, active asthma, or other potential high-risk factors. In a cost-effectiveness simulation, prescription of EAI to all patients on SCIT was not cost-effective compared with prescription only to patients with prior systemic reactions to SCIT.[268] In the United States, 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.[269,270]

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 examples of low-risk vs higher-risk histories in Table 17. 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 severe anaphylaxis (eg, comorbid asthma) or the potential benefits of having epinephrine available should anaphylaxis occur (eg, 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 (eg, to RCM or drugs) may have less need for epinephrine prescription, but they will still benefit from allergist assessment to clarify their risk and provide counseling on possible precautions.

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

Recommendation 24 (CBS): We suggest that in jurisdictions where single-packs of EAIs are available, clinicians consider a patient's risk factors for severe anaphylaxis, their values and preferences, and contextual factors when deciding whether to prescribe only one vs multiple EAIs. We suggest that they routinely prescribe more than 1 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 after 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 1 dose of epinephrine, regulatory agencies including the FDA have recommended that patients at risk of anaphylaxis carry 2 EAIs at all times.[271] In the United States, 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.[272] Shaker et al[272] used Markov modeling to evaluate and compare the cost-effectiveness of different prescribing strategies for patients with peanut allergy. They evaluated the following: (1) routinely prescribing 2 EAIs to all patients with peanut allergy; (2) prescribing 2 EAIs only to patients with a history of anaphylaxis; and (3) prescribing 2 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 United States (lowest estimated retail price of $340 for a twin-pack) and with low reported rates of anaphylaxis requiring multiple doses to treat, universally prescribing 2 EAIs is not cost-effective and has marginal health benefits compared with a risk-stratified approach.[272] They found that universally prescribing multiple EAIs would only be cost-effective in the United States 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 health care settings.[271] In children, milk-induced reactions are more likely to require multiple doses of epinephrine.[207,273] Risk factors and cofactors for severe and fatal anaphylaxis are listed in Table 18.[51,274–280] 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

Table 18
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 y • 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

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

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 18 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.[281] One rationale for prescribing multiple EAIs is the potential need for a backup unit if there is a misfire or misuse of the first unit.[282] Misuse can be mitigated by early and repeated education on correct handling and use of the specific device dispensed to the patient. Furthermore, the potential for monitoring at home without activating EMS after administration of the first dose of epinephrine requires the availability of an additional dose of epinephrine (see Recommendation 26).

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. In the United States, one of the most pressing contextual constraints is that EAIs are currently only sold in twin-packs. Moreover, some children attend schools that require them to store 1 or more EAIs on site rather than carry EAIs to and from campus each day. Such children may require 2 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 not to give epinephrine preemptively 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 vs 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 after an anaphylaxis to increased risk of biphasic reactions[3] and hospitalization.[196,283,284] In fatality case series, most patients who died from anaphylaxis did not receive timely treatment with epinephrine.[119,202,203,285] One case series of fatal anaphylaxis found that the median time interval from allergen exposure 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.[202] 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 epinephrine treatment vs without epinephrine treatment.

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 preemptive epinephrine use in cases when a patient has a known ingestion to an allergen without symptoms.[120] The absolute protective effect of preemptive epinephrine use in the absence of symptoms was low and not cost-effective.[120] 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 after 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 after epinephrine use if anaphylaxis is severe, fails to resolve promptly, fails to resolve completely or nearly completely, or returns or worsens after 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 (ie, call 911) when anaphylaxis occurs, even if epinephrine is administered and symptoms resolve.[286–288] However, there is a lack of evidence revealing the benefits of universal EMS activation. In 2019, Shaker et al[125] modeled the health and economic outcomes associated with reflex activation of EMS immediately after epinephrine use, compared with a "watchful waiting" approach, in which patients or caregivers only activate EMS afer 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 1 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

Home observation following first dose of epinephrine	Signs and symptoms that had emerged prior to epinephrine administration resolve within minutes of epinephrine administration, without recurrence, or the patient is asymptomatic. Patients with scattered residual hives or other rash (including erythema), even those with newly emerging but isolated hives or erythema without other symptoms occurring after epinephrine administration may be observed at home provided no additional new symptoms develop.
Consider EMS activation and possibly second dose of epinephrine but may continue to observe at home if comfortable	Signs and symptoms that had emerged prior to administration of the first dose of epinephrine are improving or resolving within minutes of epinephrine administration. For example, persistence of a mild sensation of globus, nausea, coughing, or stomachache may be closely observed at home provided symptoms are improving (not worsening and are perceived to be getting better) and do not persist for longer than 10-20 minutes without any additional signs of improvement.
Activate EMS immediately, consider second dose of epinephrine, do not observe at home	Signs and symptoms that had emerged prior to epinephrine administration are not resolving. Particularly concerning symptoms would include respiratory distress, stridor, altered consciousness, cardiovascular instability, cyanosis, or incontinence not typical for their age. This would also include non-skin symptoms that fail to resolve or worsen, including but not limited to repeated (>2 total) episodes of vomiting, persistent hoarseness, cough, dysphagia, wheezing, or lightheadedness.

Figure 5. General guidance for activation of EMS and administration of a second dose of epinephrine. EMS, emergency medical services.

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, health care resource use, and the need for short-term health care service rationing led allergy specialists to review and revise their recommendations around EMS activation.[3,126] Casale et al[126] implemented many of the findings of Shaker et al[125] 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[126] recommended that EMS should be immediately activated on recognition of anaphylaxis. For patients they considered to be at lower risk, they recommended 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 (Fig 5).

Casale et al[126] recommended careful monitoring for recurrence, with non-urgent follow-up care if there was prompt and complete resolution of severe symptoms after epinephrine use and if patients had ready access to additional EAIs. Patients with a history of progressively severe or biphasic reactions may require more careful or prolonged observation, as may those with comorbid conditions that may affect response to anaphylaxis and treatment. The recommendations of Casale et al[126] 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[129] have re-evaluated these recommendations for extended application beyond the contingencies of the pandemic and discuss the considerations for and against home management (Table 19).

To date, "immediate" and "prompt" anaphylaxis resolution times have not been objectively defined. For epinephrine, researchers have not yet determined the optimal time to peak plasma concentration (Tmax), time to pharmacodynamic (PD) parameter response, nor the optimal peak plasma concentration (Cmax) required for symptom resolution. Classic epinephrine pharmacokinetic (PK) data suggest that the Tmax is not more rapid than 12 to 15 minutes, and more recent data suggest that this may more reliably occur at 15 to 25 minutes.[289] However, some PD data suggest that mean increases in systolic blood pressure occur less than 5 minutes after intramuscular epinephrine injection, and anecdotally, many clinicians have observed patients responding (sometimes completely) within a few

Table 19
Considerations for and Against Home Management of Anaphylaxis

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
• Familiarity with the EAI device administration technique	• Lack of technical proficiency with administration of EAI • Hesitance about the intramuscular injection (needle phobia)
• Clear understanding of the benefits of early epinephrine treatment in anaphylaxis	• Concerns about the potential epinephrine adverse effects
• Good adherence to previous treatment recommendations, for example, use EAI for anaphylaxis in the past or use of controller medications for chronic conditions	• Poor adherence to previous treatment recommendations, for example, not administering EAI for anaphylaxis in the past or not using controller medications for chronic conditions
	• History of severe/near-fatal anaphylaxis treated with more than 2 doses of epinephrine, hospitalization, intubation

Abbreviations: EAI, epinephrine autoinjector; ED, emergency department; EMS, emergency medical services.
NOTE. Adapted from Casale et al.[129]

minutes of injection. It is difficult to suggest a specific duration of time to wait before a second dose of epinephrine is administered and EMS is called. However, we recommend the following pragmatic approach to gauge whether a reaction is resolving and as a guide for when to observe at home, administer a second dose of epinephrine, or activate EMS (Fig 5):

1) Observe at home if signs and symptoms that had emerged before epinephrine administration resolve within minutes of epinephrine administration, without recurrence, or if the patient is asymptomatic. Patients with scattered residual hives or other rash (including erythema), even those with newly emerging but isolated hives or erythema without other symptoms occurring after epinephrine administration, may be observed at home provided no additional new symptoms develop.
2) Consider EMS activation and possibly a second dose of epinephrine, or may continue to observe at home if comfortable, if signs and symptoms that had emerged before administration of the first dose of epinephrine are improving or resolving within minutes of epinephrine administration. For example, persistence of a mild sensation of globus, nausea, coughing, or stomachache may be closely observed at home provided symptoms are improving (not worsening and are perceived to be getting better) and do not persist for longer than 10 to 20 minutes without observing additional signs of improvement. Multiple contextual factors (Table 19) may influence a patient or caregiver's decision whether to administer a second dose of epinephrine and contact EMS or continue observing without further intervention.
3) Activate EMS immediately and consider a second dose of epinephrine (do not observe at home) if signs and symptoms that had emerged before epinephrine administration are not resolving or are worsening. Particularly concerning symptoms would include respiratory distress, stridor, altered consciousness, cardiovascular instability, cyanosis, or incontinence not typical for their age. This would also include non-skin symptoms that fail to resolve or worsen, including but not limited to repeated (>2 total) episodes of vomiting, persistent hoarseness, cough, dysphagia, wheezing, or lightheadedness.

The workgroup recognizes that perceptions of anaphylaxis severity may vary from one individual and context to another. A guide to severity grading of hypersensitivity (including non-anaphylactic) reactions is presented in Table 9. When developing an anaphylaxis management plan and determining an individualized set of conditions for when contacting EMS is recommended or may not be required, clinicians should engage patients in a shared decision-making process that considers individual risk factors, values, and preferences. Given variability in contextual factors, there is not likely a single universal approach for all patients and contexts.[290]

This recommendation assumes that epinephrine has been administered promptly "at the first sign of suspected anaphylaxis" (see Recommendation 25). Delay in administration may delay or impair the response to epinephrine and should be taken into account in deciding when to activate EMS.

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 intramuscular 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 adverse 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, intramuscular epinephrine is associated with reduced risk of dosing errors and adverse events.[291,292] The adverse effects associated with EAI use are typically mild and transient, with 1 registry study reporting tremors, palpitations, and anxiety as the most common.[292] A 2018 computer simulation study found that the serious adverse event rate for EAI administration was only 0.73%.[293]

In rare cases, epinephrine use for allergic reactions can cause cardiac adverse events such as arrhythmias or myocardial infarction.[294] When cardiac adverse events do occur, they are rarely associated with intramuscular administration. One observational cohort study found that among patients treated with epinephrine in an ED, adverse cardiovascular events were reported in 4 of 316 (1.3%) intramuscular administrations.[291] In a registry-based study in Spain, potentially serious adverse events—including increased blood pressure, chest discomfort, and electrocardiogram changes—were reported in 4 of 256 (1.6%) intramuscular or subcutaneous administrations.[292] Retrospective cohort studies suggest that the risk of adverse cardiac events after epinephrine use is higher in older patients (age ≥50 years).[295,296] 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.[294,297,298] Thus, the authors of case reports, observational studies, and reviews have generally recommended prompt treatment of anaphylaxis with intramuscular epinephrine, even in people with advanced age or other cardiac risk factors.[295,299–302] 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 after epinephrine use.

Other potential adverse events after an EAI administration include lacerations and embedded needles. These injuries may result when a patient or caregiver moves during administration, the device discharges off center due to malfunction, or the needle bends after hitting a bone.[303,304] 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[303] have proposed several strategies which we present in Table 20.

Improper handling of EAIs can also lead to accidental injection and needlestick injury, frequently in the thumb or other digit.[305] One registry study found that after unintentional exposures to EAIs, most people report only minor to moderate effects.[305] In rare cases, digital ischemia after accidental injection into the thumb or other digit has resulted in digital amputation.[306] A 2020 review recommended oral phentolamine as the most effective treatment for reducing

Table 20
Proposed Strategies to Reduce the Risk of EAI-Related Injury[303]

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

Abbreviation: EAI, epinephrine autoinjector.

epinephrine-induced digital ischemia.[306] Despite the low quality of available evidence, the workgroup has judged that the desirable effects of certain interventions clearly outweigh the undesirable effects. Thus, we have issued strong consensus-based statements based on very low-to-moderate quality evidence, similar to good practice statements under the GRADE methodology.

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 United States found that 97% felt financially burdened by the cost of EAIs.[307] 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.[308,309] The cost of EAIs is substantially higher in the United States than in many other countries. In the United States, the average wholesale price of 2 EpiPens increased dramatically from $113.27 in 2007 to $730.33 in 2016.[310] In comparison, the average wholesale prices of generic EAIs, epinephrine prefilled syringes, and ampules of epinephrine are substantially lower.[310,311]

In addition to the financial burden, EAI prescription may also have psychosocial effects. Although 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.[249,250] In a 2013 Australian study, health-related quality of life was worse in children with food allergy who were provided an EAI, even after controlling for age, anaphylaxis, number of food allergies, and atopic dermatitis.[312] In contrast, a 2022 French study found no association between the provision of an EAI and worse health-related quality of life,[313] and a 2021 Japanese study found no link between EAI possession and mental health outcomes.[314] 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.[121,315,316] Ward and Greenhawt[121] 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. A 2020 study in the United States found that approximately 22% of children with food allergy, 50% of adolescents, and 36% of parents reported anxiety caused by EAIs.[250]

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 United States, including the following: 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 United States (eg, Anapen, Emerade, Jext). Devices vary in their available doses, manufacturer-indicated weight class, and design, including needle length (Table 21). They also vary considerably in cost (Recommendation 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 21
Specifications for EAIs and Prefilled Epinephrine Injection Devices

Name	Dosage (mg)	Weight class specified by manufacturer[a] (kg)	Weight class supported by practice parameter[a] (kg)	Needle length[b] (cm)	Pressure[c]
Adrenaclick	0.15	15-30	<25	1.17	High
	0.3	≥30	≥25	1.17	High
Anapen[d]	0.15	15-30	<25	1.0-1.5	High
	0.3	≥30	≥25	1.0-1.5	High
Auvi-Q	0.1	7.5-15	<13	0.64-0.89	High
	0.15	15-30	<25	1.14-1.4	High
	0.3	≥30	≥25	1.47-1.73	High
Emerade[d]	0.15	15-30	<25	1.5-1.67	Low
	0.3	≥30	≥25	2.21-2.36	Low
	0.5	>60	≥45	2.21-2.36	Low
Epipen Jr.	0.15	15-30	≤25	1.0-1.5	High
Epipen	0.3	≥30	≥25	1.3-1.8	High
Jext[d]	0.15	15-30	≤25	1.3	High
	0.3	≥30	≥25	1.5	High
Symjepi	0.15	15-30	≤25	Not published	N/A
	0.3	≥30	≥25	Not published	N/A

Abbreviations: EAI, epinephrine autoinjector; N/A, not available.
[a]The manufacturer-indicated weight classes for EAIs differ from recent recommendations from multiple professional organizations, which are described and endorsed in this practice parameter.
[b]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). Owing 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.[317]
[c]The average force required to activate an EAI varies from one brand to another. According to manufacturers' specifications obtained by Dreborg and Kim, the mean activation force in Newtons (N) is as follows: 27 N for Auvi-Q (range: 8.5-53 N), 20-22 N for EpiPen Jr. (range: 8.5-35 N), 20-21 N for EpiPen (range: 8.5-35 N), and 15-17 N for Emerade (range: 8-25 N).[318]
[d]These devices are not currently available in the United States.

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 (Table 21). In the United States, the FDA has approved 0.3 mg EAIs for patients weighing more than or equal to 30 kg, 0.15 mg EAIs for patients weighing 15 to 30 kg, and a 0.1 mg EAI (Auvi-Q) for patients weighing 7.5 to 15 kg.[319] 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 less than 15 kg.[3] A 0.5 mg EAI (Emerade) is also available in some countries for patients weighing more than 60 kg.

Using dosages specified by manufacturers, patients will receive increasingly less than the recommended dose as their weight increases.[320] To limit underdosing, the AAAAI, AAP, CSACI, and EAACI support switching to 0.3 mg at 25 kg.[2,15,269,321] The CSACI advises that clinicians may consider prescribing a 0.5 mg EAI (not currently available in USA) for people weighing more than or equal to 45 kg.[269] Among teenagers, a small randomized trial of EAI administration found no significant adverse events following intramuscular self-injection with 0.3 mg or 0.5 mg of epinephrine.[322] 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 intramuscular injection into the mid-outer thigh.[320] The mean needle length and pressure required to trigger an EAI vary from one brand to another (Table 21).[323] The needle should ideally be long enough to penetrate the deep fascia of the thigh into the muscle, but not so long that it strikes a bone or causes intraosseous injection.

The depth of delivery of epinephrine is affected by the pressure with which it is delivered, including the pressure generated by the device (propulsion) and the compression by the person administering the injection.[323,324] On the basis of ultrasound imaging measurements of skin-to-bone and skin-to-muscle distance, Dreborg et al[154,325] predicted that low-pressure EAIs (Emerade) posed no risk of intraosseous injection and low risk of subcutaneous injection. For high-pressure EAIs (Auvi-Q, EpiPen, Jext), they found that the risk varied by demographics and device. They predicted that in children weighing less than 15 kg, the risk of intraosseous 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 subcutaneous injection than other devices.[154,325] In a follow-up study, they found that injecting EAIs through thick winter clothing increased the risk of subcutaneous injection for all brands—and up to 100% for Auvi-Q 0.1 mg specifically.[317] Counseling patients to remove heavy clothing before administering EAIs may help mitigate the risk.

Dreborg et al[154] predicted that the risk of intraosseous injection was low in children weighing 15 to 30 kg and negligible in adults. Ultrasound imaging measurements suggest that among adults, the risk of subcutaneous injection is highest in obese women.[325,326] Both body mass index and sex differences in subcutaneous tissue depth may affect the risk of subcutaneous injection because women tend to have more subcutaneous fat on their thighs than men.[326–328] However, Duvauchelle et al[329] found that intramuscular injection does not seem to be an absolute requirement for EAI efficacy. Overweight women were more likely to experience subcutaneous injection (n = 10 of 12) compared with non-overweight men (n = 1 of 18).[329] However, when the researchers evaluated the bioavailability of epinephrine after an injection, the initial plasma peak was similar in both groups, and the overall bioavailability of epinephrine was higher in the overweight women.[329] There is emerging evidence that the pharmacokinetics of epinephrine may vary between individual patients and between different devices and methods used for administration.[289,330] This practice parameter addresses only injectable epinephrine; noninjectable routes of administration have been developed and have been reported to have favorable pharmacokinetic and pharmacodynamic profiles, but no clinical evidence base was available at the time of the development of this practice parameter.

Accessibility

Manufacturer shortages, patient drug coverage, and other factors may affect the accessibility of EAIs and influence providers' prescribing decisions.[311,331] 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. In the United States, EAIs are sold only in packages of 2; the cost might be reduced, and access improved, if they were available in single units. Clinicians may also consider prescribing generic EAIs as a more affordable alternative to brandname 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 vs manual epinephrine administration with an ampule/vial and syringe and found no relevant studies.[332]

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 found lower rates of error with Auvi-Q than with EpiPen Jr. or Anapen.[333,334] A 2013 study in the United States also found that children and caregivers expressed a preference for Auvi-Q over EpiPen.[335] 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.[336] When asked why they preferred a particular brand, respondents said that they found it easy to administer, the instructions on the label were clear and easy to follow, the manufacturer provided helpful resources, and/or it was the brand they had been trained on by a health care professional.

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, because of a variety of factors.[247,337] 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 reveal the benefits of clinician-provided education and counseling for improving EAI-related knowledge, skills, and comfort.[338] However, a single instructional session is not sufficient for sustained improvement.[339,340] More research is needed to identify the optimal frequency of EAI education for patients and caregivers, but 1 study in Turkey suggests that 6-month intervals may be appropriate.[341]

Possessing an EAI trainer device and practicing its use on another person have also been linked to increased rates of proper administration.[342,343] 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.[344,345] Similarly, self-injection with an empty syringe during a supervised clinic visit has been linked to improved comfort with injection among at-risk adolescents.[346] Seeing clinicians administer epinephrine for anaphylaxis during health care encounters may also reinforce the importance of epinephrine administration for patients and caregivers.[347]

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 because of 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.[348–350] Pediatric doses may degrade more quickly after expiration compared with adult doses.[350]

Despite the revealed benefits of EAI education for patients and caregivers, provision of this support remains suboptimal.[351,352] 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.[352–354] Proposed strategies to address these barriers include automated implementation of EAI teaching and comfort assessments during check-in at allergy clinics,[351,355] provision of a dedicated pharmacist who can provide counseling on medication,[352] and provision of EAI training for clinicians.[356–360] Studies have found that in-person training sessions,[360] video education sessions,[356,357] e-learning sessions,[358,361] and mixed-method training approaches[359] 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.[353] Despite the low quality of available evidence, the workgroup has judged that the desirable effects of certain interventions clearly outweigh the undesirable effects. Thus, we have issued strong consensus-based statements based on very low-to-moderate quality evidence, similar to good practice statements under the GRADE methodology.

Knowledge gaps regarding prescription and use of epinephrine for anaphylaxis are listed in Table 22.

Table 22
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 vs delayed epinephrine administration for anaphylaxis
  - outcomes after reflex EMS activation vs watchful waiting after epinephrine administration for anaphylaxis
  - optimal epinephrine dosing
  - implications of EAI needle length
  - ideal frequency of EAI training for patients and caregivers

Abbreviations: EAI, epinephrine autoinjector; EMS, emergency medical services.

Beta-Blocker and Angiotensin-Converting Enzyme Inhibitors

BB medications are widely used for a variety of cardiovascular conditions, including hypertension, arrhythmias, and congestive heart failure, and for prevention of migraine and treatment of glaucoma. These medications have physiological effects that might affect the severity of anaphylaxis and the response to treatment. BBs 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. ACEIs have similar uses to BBs for patients with cardiovascular conditions, especially in patients with diabetes. 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, BBs and ACEIs have been found 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 CVD).[362] The 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 are similar to ACEIs with respect to the risk of severe anaphylaxis (see specific medications in subsequent discussion). Therefore, ARBs are not addressed in this practice parameter, and anything stated about ACEIs should not necessarily be construed to apply to ARBs.

Although there is a widely held assumption that the use of BBs and ACEIs is 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.[297,363,364] 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 BBs in use were nonselective (eg, propranolol, nadolol), with many of the reports not taking into account the confounder of cardiac comorbidities that could independently account for the increased risk of severe anaphylaxis.[297] 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.

A systematic review and meta-analysis of observational studies of the relationship between anaphylaxis of all causes and use of BBs and ACEIs analyzed 22,313 episodes for severity and 18,101 episodes for incidence.[297] Both BBs and ACEIs were associated with significantly increased severity (OR = 2.19 and 1.56, respectively), but the incidence of anaphylaxis (OR = 1.40 and 1.38, respectively) was not significantly increased. The quality of evidence was low, and it was not possible to adjust for CVD 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 CVD, the OR for severe anaphylaxis in relation to CVD was 3-fold higher than the OR in those receiving BB treatment and 5 times higher than the OR in those on the ACEIs.[297]

Given the current propensity to use more cardioselective beta-blocking agents (eg, metoprolol, atenolol), and the risk/benefit ratio for each of the interventions, we recommend a shared decision-

Table 23
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 found to derive benefit from BB.	Risks include poorly controlled heart rate, inadequate secondary prevention of cardiac disease, and ongoing symptoms of CHF. Glaucoma often cannot be managed without ocular BBs but risk of systemic complications of beta-blockade extremely low. Minimal risk of avoiding BBs for migraine prophylaxis as many alternatives now exist.
What is the indication for the intervention? Skin test Initial AIT Mc AIT Initial VIT Mc VIT	Benefit of skin testing includes accurate diagnosis. Benefit of environmental AIT is mainly improved QOL. Benefit of VIT is reduction of morbidity and elimination of mortality.	Risk of avoiding skin tests includes delayed/inaccurate diagnosis. Risk of avoiding AIT includes ongoing QOL burden if pharmacotherapy has failed. Risks of avoiding VIT means ongoing risk of potentially life-threatening anaphylaxis.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIT, allergen immunotherapy; BB, beta-blocker; CHF, congestive heart failure; MI, myocardial infarction; QOL, quality of life; VIT, venom immunotherapy.

making discussion between patient, prescribers, and providers to convey the absolute and relative risk of the treatment/procedure while receiving the BB/ACEI medication, the risk of stopping the BB/ACEI medication, 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 medications, 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 found in Table 23. The clinician, the patient, and the prescriber (eg, 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.

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 because of 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 (eg, 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 medications 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.

Although it is believed that there is less potential risk with beta-1-selective blockers than with nonselective BBs, 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 cardioselective BB so as to minimize the risk, given the more targeted nature of these BBs, 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 ACEIs and ARBs. In 1 study of angioedema (n = 4511 events), the adjusted OR compared with BBs was 3.04 for ACEIs, 2.85 for the direct renin-inhibitor aliskiren, and 1.16 for ARBs.[365] 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.[366] In a study of systemic reactions to immunotherapy injections, there was no difference in the frequency of reaction between ACEI- and ARB-treated patients.[367] It should not be assumed that ARBs carry the same potential risks as ACEIs, but there is not sufficient evidence to recommend either avoidance or safety of ARBs in patients at risk for anaphylaxis. Moreover, angioedema caused by ACEI or ARB is likely due to a different mechanism than the angioedema that occurs with 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 receiving VIT may continue BB or ACEI medications 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 BBs or ACEIs?

Recommendation 32 (CBS): We suggest that VIT may be prescribed for patients with a history of insect sting anaphylaxis who are treated with BB or ACEI medication, with shared decision-

making regarding the benefits and potential harms of concurrent VIT treatment and medication, compared with 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 BBs or ACEIs, should VIT be stopped or the medication discontinued?

Recommendation 33 (CBS): We suggest, in most cases, treatment with BB or ACEI medication need 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 BBs or ACEIs was first reported in relation to insect sting allergy and VIT 30 to 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.[368–370] Müller and Haeberli[371] recognized the importance of BBs in management of CVD and studied patients with CVD and BB treatment who received VIT. During VIT buildup, 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 a BB during maintenance VIT. Thus, 25 patients were treated with a BB during VIT (all with history of severe sting anaphylaxis). Systemic symptoms occurred in 12% of the patients receiving a BB and in 11.6% of 138 patients with CVD who were not receiving a BB. There was also no difference in the rate of systemic reaction to stings during VIT in patients with CVD who were or were not treated with a BB.

Concern regarding BB and ACEI treatment in patients at risk for insect sting anaphylaxis was increased by the report of Ruëff et al[372] of 962 patients with a history of sting anaphylaxis (52 on BB and 42 on ACEI) that revealed a significantly greater severity of sting anaphylaxis in patients receiving a BB (34.6% severe vs 20.7% with no BB; $P = .024$) or ACEI (42.9% severe vs 20.4% with no ACEI; $P = .002$). A similar study by Stoevesandt et al[373] found no correlation between cardiovascular medications and the severity of sting anaphylaxis. Both groups published subsequent reports on patients receiving VIT revealing no increased risk of systemic adverse effects in patients receiving BB or ACEI medication.[374–377] It is noteworthy that both Stoevesandt et al[376] and Müller and Haeberli[371] actually found a lower incidence of adverse events in patients with CVD who were treated with a BB or ACEI than in those who were not.

More recently, there have been 2 large studies that addressed the issue of BB/ACEI treatment in patients experiencing insect sting anaphylaxis with somewhat conflicting results. Francuzik et al[378] reported a case-control study of 12,874 cases of anaphylaxis from the European Anaphylaxis Registry that characterized 3612 cases of venom anaphylaxis and 3605 matched cases of nonvenom anaphylaxis. The study found a higher frequency of severe anaphylaxis and cardiovascular symptoms in patients receiving BBs or ACEIs, but the authors cautioned that the apparent effect of the medications correlated closely with coexisting CVD, so that severe anaphylactic reactions could not be attributed specifically to the medications.[378] Conversely, in the first prospective observational study and largest study of its kind, Sturm et al[298] enrolled 1425 patients with a history of sting anaphylaxis of whom 1342 began VIT. They found that there was no increased frequency of anaphylaxis to VIT injections or to stings during VIT in 338 patients treated with 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 receiving BB and ACEI medications (OR = 1.14; 95% CI, 0.89–1.46; $P = .29$).[298] In contrast to the earlier report of Nassiri et al,[362] the data in the study of Sturm et al[298] did not reveal an additive effect of BB and ACEI treatment on the frequency or severity of anaphylaxis during VIT. Although the studies by Sturm et al[298] and Francuzik et al[378] revealed somewhat differing results with respect to severity of anaphylaxis in patients receiving BBs or ACEIs, they both revealed that the risk of reaction related to medications correlated very closely with the risk related to CVD and, therefore, could not be attributed directly to the medications. Kopac et al[379] studied biomarkers for severe insect sting anaphylaxis and found that the use of BBs or ACEIs was not associated with the severity of honey bee 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 BBs or ~~A~~CEIs. Before 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 seem to be any increased risk associated with cardiovascular medications. It is important to acknowledge that patients with CVD 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. Moreover, changing the medication may lead to increased morbidity or mortality from the underlying CVD, 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 CVD.[380] Although the prescribing physician may be consulted about the medical necessity of the BB or ACEI medication, they should only be changed when there is an alternative medication that is safe and 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 (eg, BBs for post-myocardial infarction, congestive heart failure, high blood pressure, glaucoma, or migraine) and its benefit and risk, the values and preferences of the patient, and the relative efficacy of non-BB or non-ACEI alternatives. Underlying CVD 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.[237] Therefore, the recommendations for patients with insect sting allergy may differ from those for other immunotherapy patients.

Allergen Immunotherapy

Question: Should patients who are treated with BB or ACEI medication 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 medication, with shared decision-making. It would be preferable to replace the BB or ACEI, if there is a 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 medication, should AIT be stopped or the medication discontinued?

Recommendation 35 (CBS): We suggest that patients receiving maintenance dose AIT have a minimal increased risk of a severe anaphylactic reaction when on BB/ACEI medication 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 BBs or ACEIs in patients undergoing SLIT has not been associated with increased severity or frequency of systemic allergic reactions.[381,382] Beta-blockers are not associated with increased frequency of systemic reaction to SCIT; however, evidence from VIT, cases reports, and a SCIT surveillance program suggests that these medications may increase severity of reaction in patients receiving SCIT.[381–383] In fact, in a survey of the experience and opinion of physicians, 37.1% and 47.3% report prescribing AIT in patients receiving BBs and ACEIs, respectively, and none reported major anaphylactic incidents during the course of the treatment.[384] There is also no specific evidence related to the risk of BB/ACEI medication during buildup SCIT compared with maintenance SCIT. However, when the baseline risk of reaction is higher (as is expected during the buildup schedule), then the risk of a more severe reaction related to BB/ACEI medication might also be expected to be higher.

The available evidence is not specific to SCIT but rather was common to studies of many or all causes of anaphylaxis. The theoretical risk of BB treatment was not confirmed in a study of anaphylaxis in the ED revealing they were not associated with an increased need for epinephrine.[363] However, a recent systematic review of anaphylaxis of all causes found that the risk of severe anaphylaxis was significantly increased but the incidence of new cases of anaphylaxis was not.[297] Furthermore, it was not possible to adjust for underlying CVD, and in fact, the risk of anaphylaxis was 3 to 5 times higher in patients with known CVD than in those taking BB/ACEI medication. It is important to note that although the relative risk may be increased, the absolute risk remains very small. For example, the frequency of systemic reactions to SCIT is approximately 0.2% for each injection, most of which are mild-moderate (ie, severe reactions occur in <0.1% of injections).[71] Even if the relative risk of a severe reaction is 2-fold higher as reported in patients taking a BB or ACEI, the absolute risk would still be very low (<0.2%). 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, including the patient's history of anaphylaxis and associated risk factors, in the framework of the available evidence.

Planned Procedures: (eg, Drug Desensitization, Radiocontrast Media Administration, Intravenous Immunoglobulin Infusion)

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

Recommendation 36 (CBS): For planned procedures (eg, RCM, challenge/desensitization, and infusion) if the BB/ACEI medication 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 medications 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 BBs and ACEIs.[385,386] However, 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 medications increase the severity of anaphylaxis after RCM administration. In a case-control study of 34,371 intravenous RCM procedures by Lang et al,[387] BB exposure and CVD were highly associated (X^2 = 49; P < .001). Using a logistic regression model with adjusted ORs, increased risk of bronchospasm was associated with BB (OR = 3.73, 1.18-11.75; P = .025) and asthma (OR = 16.49, 4.30-62.46; P = .001), independent of CVD. Of 21 reactors with CVD who did not have asthma, 10 were receiving BB; 9 of these 10 had bronchospasm compared with only 4 of 11 not receiving BB (OR = 15.75; P = .023). Risk of a major and life-threatening reaction (hypotension with/without need for hospitalization) was associated with CVD (OR = 7.71, 1.04-57.23; P = .046), independent of asthma or BB exposure. A more recent case-control study of patients receiving intra-arterial low-osmolality contrast during cardiac catheterization found no increased rate of severe anaphylactic reactions in association with BBs (P = .40) or ACEIs (P = .14).[366] However, in that study of 71,782 cardiac catheterizations, only 11 cases (0.015%) of severe anaphylaxis were observed—reflecting the substantial reduction in severe adverse reactions with low osmolar contrast. Neither cardioselective BBs (P = .2) nor non-cardioselective BBs (P = .5) influenced reaction severity.[366]

Anaphylaxis can occur during IVIG infusions; however, this is a very rare complication (7.34 per 10,000 infusions).[388–390] 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.[391] In a study of patients with idiopathic inflammatory myopathy and concomitant heart failure, 75% of patients receiving IVIG therapy were using BBs and/or ACEIs. In these patients, no cases of anaphylaxis were reported.[389] Literature on the relative risk of anaphylaxis in patients receiving IVIG while on BB or ACEI medication 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 medication be stopped or continued?

Recommendation 37 (CBS): We suggest that all patients at significant risk for recurrent and unexpected anaphylaxis (eg, those with severe food allergy, mastocytosis or MCAS, or recurrent IA) be counseled about the risk of more severe anaphylaxis, and consider avoiding, where possible, the use of nonselective BBs or ACEIs.

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 (eg, 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 (before VIT). There could reasonably be increased concern in these patients for the potential risk associated with BB or ACEI medication.

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.[392] 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 BBs or ACEIs in patients with IA, but the reported increased risk of severe reactions that has been associated with BBs and ACEIs 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 treatment may increase severity, they are less important than age as a risk factor for severe anaphylaxis.[393] Tenbrook et al[380] studied a simulated cohort of adults with peanut allergy and underlying CVD. 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 BBs. 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.[380] Furthermore, with the assumptions in this model, BBs were preferred unless the annual rate of moderate-to-severe anaphylaxis exceeded 6% for patients with post-myocardial infarction and 15% for patients with congestive heart failure. 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.[394] Similar analyses have not been conducted for IA, MCAS, alpha-gal allergy, or HαT. Overall, before stopping BBs in patients with a history of anaphylaxis, the relative risk of CVD without BB treatment must be weighed against the risk of more severe anaphylaxis while on BB treatment[395] and requires a shared decision-making discussion.

Summary of Recommendations for Beta-Blocker/Angiotensin-Converting Enzyme Inhibitor Medication

In summary, clinicians should weigh the potential benefits and harms when considering the use of BBs and ACEIs in patients at risk for anaphylaxis (Table 23). 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 (eg, cardiologist).

Patients taking BBs or ACEIs 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 buildup 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 BBs and ACEIs 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 medication in patients at risk for anaphylaxis are listed in Table 24.

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 most patients.[396] Mast cell activation, in its most severe form, may present with anaphylaxis. It has been estimated that approximately 40% to 50% of adults and 10% of children with mastocytosis experience anaphylaxis.[397] Risk factors for anaphylaxis associated with mastocytosis include male sex, total serum IgE greater than 15 kU/L, atopic background, and tryptase levels less than 42 ng/mL.[398] New potential biomarkers for risk of anaphylaxis in patients with mastocytosis have been reported.[399] Anaphylaxis is also overrepresented in patients with mastocytosis who lack skin lesions; however, it is not clear whether this finding is due to referral bias. Most 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.[400,401] The

Table 24
Knowledge Gaps Related to Use of BB or ACEI Medication in Patients at Risk for Anaphylaxis

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

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker.

Table 25
WHO-Proposed Refined Major and Minor SM Criteria

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 level 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

Abbreviations: bST, baseline serum tryptase; HαT, hereditary α-tryptasemia; SM, systemic mastocytosis; WHO, World Health Organization.
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[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.[405]
[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.

prevalence of drug, food, and POA is also slightly increased in mastocytosis.[402]

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 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 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 WHO for cutaneous and systemic mastocytosis are detailed in Table 25.[403–405] Diagnosis requires at least 1 major and 1 minor or 3 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.[403] Differential diagnoses of conditions which can be associated with elevated bST levels are listed in Table 26, and the clinician should be aware that this marker is not specific for a mast cell disorder.[403,406] Moreover, there should be awareness that the differential diagnosis of an elevated bST level includes HαT, which is an autosomal-dominant genetic variant caused by increased copy numbers of alpha tryptase genes encoded by TPSAB1 locus.[83] 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% to 7% of the general population and is most frequently asymptomatic but is reported in more than 15% of patients with IA, mastocytosis, or insect sting anaphylaxis.[91,407] It is not clear whether this is because of selection bias or a yet to be defined mechanism affecting mast cell proliferation or activation. HαT is discussed in more detail in the Diagnosis section.

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.[403] 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 on being rubbed. Documentation of a thorough skin examination with pertinent positive and negative findings is of high importance.[403] Isolated cutaneous mastocytosis is very uncommon in adults. The risk of anaphylaxis in children with cutaneous mastocytosis (in whom systemic disease is uncommon) is believed to be much less than in patients with systemic mastocytosis, ranging from 0% to 9% in various studies, and mainly occurs in those with extensive skin involvement and higher tryptase levels.[408]

Key presenting symptoms of systemic mastocytosis will overlap with anaphylaxis but also may include the aforementioned skin findings, presyncope/syncope, constitutional symptoms (eg, fevers, weight loss, night sweats), bone pain, and prominent gastrointestinal symptoms such as reflux, nausea, vomiting, diarrhea, and colic. On physical examination, hepatosplenomegaly and lymphadenopathy may be prominent especially in patients with advanced disease. Multiple reviews detail the key presenting features of mast cell disorders.[396,403,404,409] 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

Table 26
Differential Diagnosis for Elevated Baseline Serum Tryptase Level

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

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detailed previously, displays increasing tryptase levels, and the cutaneous lesions fail to regress by puberty.[410–412]

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 and for staging to determine whether the disease is advanced. Although mast cell proliferation can be noted in most other affected organs, the marrow remains the most important area for biopsy.[404] 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.[95,413] A KIT mutation analysis is also generally ordered with most bone marrow aspirates and is more sensitive than peripheral blood mutational analysis.[414] 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% to 90% sensitivity compared with bone marrow biopsy and more than 99% specificity. It is important to note that tests frequently used in hematologic neoplasms based on next-generation sequencing are not sufficiently sensitive.[414] Nonetheless, in a patient with symptoms suggestive of 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 D816V mutation using a highly sensitive allele-specific PCR or digital droplet PCR-based technique, and whether there is peripheral eosinophilia, a FIP1L1-PDGRA mutational analysis.[403,404] In some cases, biopsy of other extracutaneous organs may be helpful, as described in WHO guidelines, most frequently by gastrointestinal mucosal biopsy.[415]

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 be continued indefinitely in patients with mastocytosis and insect sting anaphylaxis 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 been found to have a unique association with mastocytosis.[416] Furthermore, an unusually high frequency of clonal mast cell disorders has been found in patients with severe sting anaphylaxis.[417,418] Venom anaphylaxis in patients with mastocytosis is associated with a unique clinical pattern of reaction and with a unique phenotype of mastocytosis.[419,420] The frequency and clinical characteristics of mast cell disorders in patients with insect sting allergy in the United States may differ from those in European reports.[421] The presentation of insect sting allergy that is most suggestive of 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 test results for venom IgE had a very high risk (93%) of severe and life-threatening anaphylaxis to insect stings.[422] This led the authors of that report to suggest that testing for venom IgE should be considered in all patients with mastocytosis and that those with positive test results should be offered VIT (even if they have never had a systemic reaction to a sting).[422] 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 level is unusually common in patients with insect sting anaphylaxis.[423–425] 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.[378] 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%).[91] However, one study found venom anaphylaxis correlated with presence of D816V mutation-positive clonal mast cells rather than HαT.[413] In that population of patients with severe insect sting anaphylaxis who had positive test results for D816V mutation by high sensitivity PCR blood test, 28 of 34 (82%) had normal tryptase levels.[413]

Although once considered too dangerous, VIT is now recommended in patients with mastocytosis with insect sting anaphylaxis.[237,401] 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.[426] During maintenance VIT, systemic reactions to stings occur in 5% to 15% of patients without mastocytosis but in 25% of patients with mastocytosis.[427] This still represents significant benefit because, without VIT, the risk of sting reactions in patients with mastocytosis and prior systemic reaction to a sting is more than 75%.[422] 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.[428] In patients who have repeated reactions to VIT, omalizumab has been reported to enable most patients to achieve maintenance dose.[429,430] 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.[422,426,431] It is, therefore, recommended that patients with mastocytosis should continue VIT indefinitely.[237,401]

Clinical Presentation

Anaphylaxis manifestations in mastocytosis frequently 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.[93] 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 Fig 4), risk-stratification schemes for the probability of mastocytosis in patients presenting with mast cell activation symptoms have been proposed by REMA and NICAS.[93,94,96] 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. 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 to 5 ng/mL in the general population. Elevated bST levels can be found in chronic renal failure, myeloid disorders, and HαT. Although a cutoff level of "normal" tryptase 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 less than 8 ng/mL.[432] 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).[433] Detection of this mutation in the 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 previously, 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 consisted of a broad range of disorders with various etiologies presenting with systemic mast cell activation. They can be classified as primary (clonal; eg, mastocytosis), secondary (eg, IgE mediated), or idiopathic. Mast cell activation and mediator release are the primary cause of the manifestations 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 the following 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 the Diagnosis section] for the minimal diagnostic increase in a post-event tryptase obtained within 4 hours); and
3. Positive response to mediator-targeting drugs.[79,434,435]

Chronic and nonspecific multiorgan symptoms and patients with multiple environmental and food intolerances without meeting these criteria should not be diagnosed with having 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.[436] A randomized clinical trial revealed a promising trend, but the results were not significant in a small group of 19 patients with severe IA.[437] 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.[438] 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.[439–441] Carter et al[442,443] 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 patients with mastocytosis 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%).[444]

Omalizumab is not currently approved by the FDA in the United States 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 tyrosine kinase inhibitors (TKIs), may be more likely to be effective.

Mast Cell Cytoreduction and Tyrosine Kinase Inhibitors

There is evidence that mast cell cytoreduction (reduction of mast cell mass) results in improvement of anaphylaxis in mastocytosis. In 1 study, use of cladribine (an antimetabolite purine analogue) for treatment of advanced or indolent mastocytosis resulted in complete clearance of anaphylactic episodes.[445] D816V KIT mutation associated with mastocytosis results in constitutive activation of the tyrosine kinase function of the molecule. As such, TKIs targeting D816V KIT have been considered a first-line approach for mast cell cytoreduction, given toxicities associated with cladribine. Although cytoreductive therapy has been traditionally reserved for patients with advanced mastocytosis, recent emergence of TKIs with low toxicity profiles has made this treatment an attractive possibility for those presenting with mast cell activation symptoms inadequately controlled with symptomatic therapies.[446] Midostaurin and avapritinib are the TKIs currently FDA approved for treatment of advanced mastocytosis, conditions that are associated with decreased life expectancy (ie, aggressive systemic mastocytosis, systemic mastocytosis with an associated hematologic neoplasm, and mast cell leukemia). The mast cell cytoreductive effects of these TKIs are associated with symptom control of mast cell activation.[447–449] Avapritinib is now also FDA approved for indolent systemic mastocytosis, at a lower daily dose. Neither drug is approved for prevention of anaphylaxis.

Midostaurin is a multikinase inhibitor whose targets include wild-type and D816V-mutated KIT. It has been found 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.[450] It should be noted that these drugs require periodic monitoring with complete blood cell count with differential and are contraindicated in pregnancy. An open-label trial of midostaurin in indolent systemic mastocytosis revealed significant reduction of symptoms due to mast cell activation, but nausea and vomiting are common adverse effects of the drug.[451]

Avapritinib, a selective D816V KIT inhibitor, is approved by the FDA for treatment of patients with advanced systemic mastocytosis.[448,449] 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.[452] Avapritinib has recently been approved by the FDA for symptomatic indolent systemic mastocytosis based on the results of a randomized controlled trial (ClinicalTrials.gov identifier:

Table 27
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 mast cell activation symptoms, and if so, what are the mechanisms for it?
- In determining whether HαT is a risk factor for anaphylaxis in general (and for which triggers), 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 result? If so, to which venoms?
- Is preemptive 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?

Abbreviations: HαT, hereditary α-tryptasemia; TPSAB1, tryptase α/β-1; VIT, venom immunotherapy.

NCT03731260) of a lower daily dose that revealed reduction of mast cell activation symptoms and all measures of mast cell burden.[453] Avapritinib is contraindicated in patients with platelet counts of less than 50,000/μL. Other KIT D816V selective TKIs currently being evaluated in clinical trials include elenestinib (BLU-263; NCT04910685) and bezuclastinib (NCT05186753). In patients with mastocytosis and recurrent episodes of anaphylaxis despite optimal medical therapy with high-dose H_1 antihistamines and H_2 antihistamines (and possibly a trial of omalizumab), consideration may be given to a trial of avapritinib or compassionate use of midostaurin, or referral to a clinical trial for a TKI, although neither is currently FDA approved specifically for prevention of anaphylaxis.

Knowledge gaps related to anaphylaxis in mastocytosis are listed in Table 27.

Perioperative Anaphylaxis

POA 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.[454] POA has a greater risk of death than other forms of anaphylaxis.[455,456] In a multivariate analysis of POA cases, independent risk factors associated with a fatal outcome related to NMBAs, despite treatment with epinephrine, were as follows: male sex (OR = 2.5; 95% CI, 1.4-5.0; P = .0004), emergency surgery (OR = 2.6; 95% CI, 1.5-4.6; P = .0007), history of hypertension (OR = 2.5; 95% CI, 1.5-4.4; P = .0010) or other CVD (OR = 4.4; 95% CI, 2.4-8.1; $P < .0001$), obesity (OR = 2.4; 95% CI, 1.1-5.3; P = .0376), and BB exposure (OR = 4.2; 95% CI, 1.8-9.8; P = .0011).[457] Increased risk for POA has also been associated with transplant, cardiac, vascular, and hematologic procedures.[454] Recent trends in POA include the recognition of geographic variation in etiologic agents (perhaps based on different preprocedure exposures to sensitizing factors), a declining incidence of POA due to latex, and a greater appreciation for reactions related to antibiotics—particularly cefazolin.[458–460] 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 blinded 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.[459,460] A retrospective study revealed that serious anaphylaxis during anesthesia was associated with elevations in serum tryptase level (mean = 86.5 ng/mL); moreover, tryptase level elevation was not observed in a comparator group with cardiogenic or septic shock but no anaphylaxis who were resuscitated.[459] These data imply that resuscitation itself cannot account for serum tryptase level elevation. However, serum tryptase level is not always increased in anaphylaxis, even in severe or fatal reactions. A French study of POA reported an increase in serum tryptase level in 68% of suspected IgE-mediated POA but in only 4% of non–IgE-mediated POA.[461] Elevations in serum tryptase level are most often detected in cases of anaphylaxis that involve hypotension and in reactions that are IgE mediated.[22,454,458,461] The sensitivity (64%) and specificity (89%) of elevated serum tryptase level (>11.4 ng/mL)[460] lead to a calculated positive likelihood ratio (LR) of 6 and a negative LR of 0.4. These LRs indicate that an elevated serum tryptase level gives moderate support to the likelihood of POA, but a lack of increase in serum tryptase level should not be interpreted as ruling out a diagnosis of POA.

Measurement 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 after 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.[22,461]

Interpretation of serum tryptase level is based on international consensus recommendations noting a 1.2-fold increase plus 2 ng/mL, consistent with degranulation of mast cells during the suspected reaction.[432] Because bST values may be more variable in patients with mastocytosis or HαT, 1 study found optimal sensitivity and specificity with a threshold acute/baseline tryptase level of 1.685 (further discussed in the Diagnosis section).[80] The timing of obtaining the serum sample is important. The concentration peaks within 30 to 60 minutes of the reaction and then typically returns to baseline in 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.[462] Tryptase is stable for as long as 1 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[463]; in 139 (77%) with clinical POA, an increase of tryptase level (>1.2 × baseline + 2 μg/L) was observed. Severity of anaphylaxis was associated with a tryptase level 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 (ie, IgE mediated or not IgE mediated). A number of perioperative drugs, including paralytics (NMBAs), opioids, and antibiotics (eg, vancomycin), can induce mast cell degranulation independent of IgE.[22,459,460,464] To determine whether serum tryptase level is increased after 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.[432] The baseline level should be determined even if the acute-phase tryptase result is normal. Diagnostic evaluation of patients with persistent elevations of tryptase level 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 nonpharmacologic 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 be performed, when available, to all potential pharmacologic and nonpharmacologic culprits used during the perioperative period. If testing is not possible, we suggest referral to another center or, if necessary, use of the most efficacious agents structurally dissimilar from the most likely culprit.

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,[458,460] but the limited reliability and validity of testing to these agents make 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 pretesting causes for POA, these were not confirmed in 73% of the cases, resulting in a poor correlation between clinical impression and the results of diagnostic evaluation.[465] These data suggest that testing for *all* potential culprits is required in the evaluation of patients with POA. Furthermore, 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 and any alternative NMBA agents available at that health care facility. Although of limited reliability, the negative predictive value of the skin tests may assist in the choice of NBMA in affected patients.

Published resources provide empirical, nonirritating concentrations for hypersensitivity skin testing of potential culprit pharmacologic causes of POA, as found in Table 28.[458,466–470] The positive and negative LRs of such testing have not been determined. A positive skin test result implies greater risk for IgE-mediated reaction with reexposure, 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 with a positive skin test result would likely be in a patient's best health care interest, if equally efficacious, structurally unrelated alternatives are available. Data reveal that administration of agents with negative test results can proceed safely, suggesting that testing may be helpful in drug selection for subsequent anesthesia (Table 29).[471–473] Just as we do with many other allergens to which skin testing result is negative (eg, latex, lidocaine, chlorhexidine, povidone-iodine), as the sensitivity (or negative likelihood ratio) is not well established, we may carry out provocative challenges to definitively rule out IgE-mediated (allergic/anaphylactic) potential. For some agents (eg, NMBAs, midazolam, propofol), it would be appropriate for an anesthesiologist to administer them in a graded dose (ie, "test dose") fashion immediately before the planned procedure.

Table 28
Recommended Concentrations for Skin Tests: Skin Prick Tests and Intradermal Tests[458,466–470]

Item for testing	SPT concentration	IDT concentration
NMBAs		
Atracurium[466]	1 mg/mL	0.01 mg/mL
Cisatracurium[467]	2 mg/mL	0.02 mg/mL
Mivacurium[468]	0.2-1.0 mg/mL	0.002-0.01 mg/mL
Pancuronium[468]	2-20 mg/mL	0.2-2 mg/mL
Rocuronium[467]	10 mg/mL	0.05 mg/mL
Vecuronium[467]	1 mg/mL	0.01 mg/mL
Succinylcholine[467] (Suxamethonium)	20 mg/mL	0.8 mg/mL
Hypnotics[466]		
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	0.05 mg/mL
Opioids[a,466]		
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[467]	100 mg/mL	50 mg/mL
β-lactams		
Pen G (10,000 U/mL)[458]	Undiluted	Undiluted
Benzylpenicilloyl Polylysine (Prepen)[458]	Undiluted	Undiluted
Ampicillin[458]	20 mg/mL	20 mg/mL
Cefazolin[469,470]	20 mg/mL, 33 mg/mL	20 mg/mL, 33 mg/mL
Local anesthetics[466]	Undiluted	1/10
Heparins[466]	Undiluted	1/10
Tranexamic acid[466]	Undiluted	1/10
Protamine[466]	Undiluted	1/1000-1/10,000
Aprotinin[466]	1/5	1/500
Hyaluronidase[466]	Undiluted	1/10
Antiseptics[466]		
Povidone iodine[468]	100 mg/mL	Not recommended
Chlorhexidine[468]	5 mg/mL	0.002 mg/mL
Dyes		
Patent blue (25 mg/mL)[468]	1:10, Undiluted	1:100, 1:10
Isosulfan blue[468]	1:10 dilution, undiluted	1:1000, 1:100, 1:10
Methylene blue[468]	Undiluted	0.1 mg/mL
Neostigmine[467]	1 mg/mL	0.2 mg/mL
Methohexital[468]	1 mg/mL	0.1 mg/mL

Abbreviations: IDT, intradermal test; NMBA, neuromuscular blocking agent; Pen G, penicillin G; PPL, penicilloyl polylysine; SPT, skin prick test.
[a]Hypersensitivity skin testing to opioids may be unreliable due to high rates of false-positive results.

Availability of drugs for testing is limited by the controlled nature of many agents used in anesthesia and distribution exclusively by inpatient pharmacies. Albeit very small amounts of the drugs are needed for testing, the acquisition of samples is often unobtainable due to geographic, logistic, and legal barriers. These issues are generally less of a problem in some integrated health care 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. On the basis of 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

Table 29
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,[471] 2011	606	246	183	183	0
Guyer et al,[472] 2015	73	73	47	45	2
Miller et al,[473] 2018	174	70	70	67	3
Total	853	389	300	295	5 (1.7%)

Abbreviation: POA, perioperative anaphylaxis.

performed as soon as possible or delayed 4 to 6 weeks after the POA event?

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

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

Delaying immediate hypersensitivity skin testing for 4 to 6 weeks after anaphylaxis is generally suggested. This is based on case series and case reports of insect allergy, drug allergy, and POA.[474,475] 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.[476] In their study, skin testing was performed within 1 week and 4 to 6 weeks after a Hymenoptera systemic sting reaction. In 21% of the cases, the second evaluation, performed 4 to 6 weeks after, was required to confirm the diagnosis of Hymenoptera venom anaphylaxis. This phenomenon may be due to a generalized mast cell hyporesponsiveness (a.k.a., "the empty mast cell syndrome") or may be allergen specific after an anaphylactic reaction.[477]

Variability in the results of evaluation after POA is supported by a study that compared the results of skin testing at 2 time points in patients with POA,[478] the first within 4 days of the reaction and the second, 4 to 8 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. On the basis of 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 result, 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 hyporesponsiveness 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.[476–478] However, there may be a need for repeat anesthesia sooner than 4 to 6 weeks after the sentinel POA, especially because 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 health care providers to support a shared decision-making process that includes the values and preferences of the patient (and family). Furthermore, testing for available alternatives to highly suspected culprit agents may be considered. 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 nonpharmacologic culprits to which skin and/or in vitro testing is negative?

Recommendation 45 (CBS): We suggest that challenges be performed, when feasible, to all potential culprit agents to which skin and/or in vitro testing is negative, before or in conjunction with use of these agents for a future surgical procedure.

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,[479] similarly, the reference standard for evaluation of POA also entails carrying out challenges to items for which skin and/or in vitro testing result 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 result are avoided in favor of alternative agents that are structurally unrelated or which have 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 Mas-related G-protein coupled receptor member X2 (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.[480] However, the role of MRGPRX2 receptor activation on mast cells as a cause of anaphylaxis is not certain.[481]

Graded challenge with suspected agents for which skin testing result is negative may also be carried out in collaboration with an anesthesiologist, and if necessary and feasible, in the operating room in conjunction with a planned procedure.[482] 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 through administration of a 10% "test dose" before 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 after appropriate evaluation of POA can be performed successfully with a very low rate of recurrence of POA.[471–473] Fisher et al[471] 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[472] 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[473] 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 found in Table 29, combining these 3 reports leads to a rate of recrudescence of POA with subsequent anesthesia of 1.7%.[471–473] These data support the contention that most 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.[458] However, the data cannot rule out the alternative possibility that most POA reactions are not reproducible, as has been found for messenger RNA COVID-19 vaccines.[483]

Question: Should repeat anesthesia after 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 nonpharmacologic agents associated with POA may be considered, regardless of test results if challenge is not feasible and if equally efficacious, structurally unrelated alternatives are available.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

When testing result for all potential culprits is negative, challenge is recommended but is not always feasible, and decisions must be made about the use of the potential culprits or unrelated alternative drugs. Immediate hypersensitivity skin testing to penicillin is validated; if testing result is positive to the beta-lactam only, and challenge for the other potential culprits is not feasible, it is acceptable to use all perioperative drugs except for the beta-lactam. 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[484] has not been performed. Latex mitigation or avoidance strategies are generally available in facilities performing general anesthesia.

Question: If results of all immediate hypersensitivity skin testing (percutaneous and intradermal) and/or in vitro-specific IgE testing (and challenge when possible) are negative to suspected POA culprit agents, should pretreatment with H_1 antihistamine and corticosteroid, with or without H_2 antihistamine and anti-leukotriene, be administered before subsequent anesthesia?

Recommendation 48 (CBS): We offer no recommendation for or against the use of pretreatment before return to the operating room in patients with negative cutaneous (percutaneous and intradermal) and/or in vitro-specific IgE testing (and challenge when possible) result 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 result followed by negative provocative challenge result, the recommendation as to whether to recommend pretreatment with H_1 antihistamine and corticosteroid, with/without H_2 antihistamine and anti-leukotriene, before returning to the operating room fulfills equipoise criteria.[485] The equipoise between pretreatment and no pretreatment implies not only balance but also uncertainty. On the basis of the core principle of equipoise,[485] we must acknowledge that 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 on 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.[486,487] 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.[3] The panel viewed both premedication and no premedication as reasonable paths and recommended a shared decision-making discussion between the patient, allergist/immunologist, anesthesiologist, and surgeon.

Knowledge gaps related to POA are listed in Table 30.

Table 30
Knowledge Gaps in Perioperative Anaphylaxis

Knowledge gap
• Positive and negative likelihood ratios for skin testing to pharmacologic and nonpharmacologic agents implicated as causes of perioperative 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 all 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. If anaphylaxis occurs through MRGPRX2 receptors, should all MRGPRX2 activators be avoided after POA with suspected MRGPRX2 mechanism? Does pretreatment reduce severity of MRGPRX2-mediated anaphylaxis?

Abbreviations: MRGPRX2, Mas-related G-protein coupled receptor member X2; POA, perioperative anaphylaxis.

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