Anaphylaxis in Practice: A Guide to the 2023 Practice Parameter Update

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This review summarizes new research developments and clinical practice recommendations for the diagnosis and management of anaphylaxis presented in the Joint Task Force on Practice Parameters 2023 Anaphylaxis practice parameter Update. It is intended to serve as a high-level summary of the 2023 practice parameter, which makes clinically impactful recommendations based on evidence that has emerged since the 2015 practice parameter. We invite clinicians to explore the full 2023 practice parameter to understand the research methods and underlying evidence that have informed the recommendations summarized here. There are new and evolving diagnostic criteria for anaphylaxis, rules for defining elevated tryptase levels, and recognition of signs and symptoms particular to infants and toddlers. The administration of epinephrine should not be used as a surrogate to diagnose anaphylaxis. Risk factors for anaphylaxis should be assessed on a case-by-case basis. Patient counseling and shared decision-making are essential to support patients' treatment decisions and capacity to manage the risk of anaphylaxis at home and in other community settings. Activation of emergency medical services after home epinephrine administration may not be required in all cases, and patients should be engaged in shared decision-making to determine when home management may be appropriate. © 2024 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2024;12:2325-36)

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INTRODUCTION

Anaphylaxis is a systemic, usually multiorgan, potentially life-threatening syndrome. The diagnosis is clinical, with no single sign or symptom being pathognomonic. Lifetime prevalence has been estimated to be 1.6% to 5.1%.[1] Ongoing research has advanced our understanding of the recognition and management of anaphylaxis in several areas, which are addressed in the recently published 2023 anaphylaxis practice parameter update.[1] The objective of this review article is to highlight new recommendations in the recently updated practice parameter on anaphylaxis (Table I) and their application in clinical practice (Table II). This review aims to provide an accessible summary of the recommendations and key changes and a succinct review of the underlying rationale. The reader should refer to the full practice parameter for more detailed methods, analysis, comments, and guidance, and for nuanced discussion of applications in clinical practice.

DIAGNOSIS

Recommendations 1 and 2

Many organizations have developed definitions and clinical criteria to aid in the diagnosis of anaphylaxis, but there is no single, universally accepted definition or criteria.[3-6] Serum tryptase is the most studied and widely used biomarker to support the diagnosis of anaphylaxis. An acute serum tryptase should be drawn within 2 hours after symptom onset whenever possible. In addition, a baseline serum tryptase (bST) should be drawn at a later time, and the change between bST and tryptase levels during the event can be used to aid in the diagnosis of anaphylaxis. In a diagnosis of anaphylaxis, the tryptase level during the acute event should be elevated above baseline. Two different calculations are currently proposed to define a clinically relevant increase. One follows an expert consensus recommendation to use an acute tryptase value that is 20% above bST plus 2 ng/mL (20% + 2) as an indication of mast cell activation.[7] The second calculation uses a serum tryptase that is 1.685

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Abbreviations used
ACEI- Angiotensin-converting enzyme inhibitor
BB- β-Blocker
bST- Baseline serum tryptase
CMD- Clonal mast cell disorder
EAI- Epinephrine autoinjector
IA- Idiopathic anaphylaxis
POA- Perioperative anaphylaxis
SDM- Shared decision-making
VIT- Venom immunotherapy

times the bST. This acute/baseline tryptase ratio can be tailored based on clinical suspicion, with a cutoff ratio of 1.868 when clinical suspicion is low and a cutoff ratio of 1.374 when clinical suspicion is high.[8]

Recommendations 3 to 5

For patients presenting with a history of anaphylaxis, the history is the most important factor for determining the next steps in evaluation. In settings where a likely trigger is evident, testing to the suspected trigger should be performed, and treatment should be tailored to the results. For patients presenting without an obvious trigger, a bST should be drawn, especially in those with a history of recurrent, severe, or idiopathic anaphylaxis (IA), even when an acute serum tryptase level is not available. The bST can help provide a diagnosis for patients who have an underlying condition such as a clonal mast cell disorder (CMD) or hereditary α-tryptasemia that may put them at risk for recurrent or severe anaphylaxis. Hereditary α-tryptasemia is an inherited increase in the α-tryptase-encoding tryptase α/β-1 gene, and it may be associated with more severe anaphylaxis or a predisposition to anaphylaxis events.[9,10] Hereditary α-tryptasemia is present in about 6% of the general population and in 10% to 20% of patients with severe anaphylaxis, IA, or insect sting anaphylaxis.[11] This diagnosis should be considered in patients with a bST greater than 8 ng/mL and recurrent or severe anaphylaxis.

Clonal mast cell disorder should also be considered in patients presenting with recurrent idiopathic or severe anaphylaxis. Most, but not all patients with CMD will have an elevated bST, and one should apply a scoring system, such as the Red Espanola MAstocitosis score, in addition to the bST when working up a diagnosis for a patient with recurrent or severe IA to help decide whether a bone marrow biopsy is warranted.[2,12] One final condition that may be a hidden cause of recurrent IA is allergy to galactose-α-1,3-galactose, because the reactions can be delayed, obscuring the triggering mammalian meat ingestion.[13] Thus, galactose-α-1,3-galactose allergy should be considered when evaluating a patient with recurrent IA in endemic areas or with a history of tick bite or exposure.

Recommendations 6 and 7

Although epinephrine is the first-line treatment for anaphylaxis, meeting diagnostic criteria is not required before the use of epinephrine, because there are clinical scenarios in which epinephrine may be warranted before a reaction is diagnosed as anaphylaxis. On the other hand, treatment with epinephrine or clinical response to epinephrine should also not be used as a surrogate marker to establish a diagnosis of anaphylaxis because there are many cases in which patients receive epinephrine for milder reactions.

INFANT AND TODDLER ANAPHYLAXIS

Recommendations 8 to 11

Infants or toddlers are generally defined as children aged less than 36 months. In this age group, food is the most common trigger for anaphylaxis. Current National Institute of Allergy and Infectious Diseases[3] and World Allergy Organization[4] anaphylaxis criteria are applicable to infants and toddlers when determining whether an allergic reaction is likely to be anaphylaxis.

In this young age group, age does not correlate with reaction severity, and often the first reaction to an allergen does not meet anaphylaxis criteria.[14,15] Based on limited epidemiologic data, the rate of infants and toddlers presenting to emergency departments with anaphylaxis is increasing; however, hospitalization rates have not increased.[16,17] Fatal anaphylaxis is a rare occurrence across all age groups.

Identifying signs and symptoms of severe reactions can be challenging in very young children because they are unable to verbalize subjective symptoms. Infants can have subtle behaviors that demonstrate symptoms.[18] For example, oral itching may manifest as tongue thrusting or rubbing of the mouth. In addition, general behavioral changes such as inconsolable crying and irritability may be observed during an allergic reaction. Although these age-specific behaviors can occur for reasons other than allergy, awareness of these additional signs can be important to early recognition of anaphylaxis in very young children.

COMMUNITY

Recommendations 13 to 15

Available data suggest that anaphylaxis most commonly occurs in the home setting for both children and adults. However, many patients have high concern about anaphylaxis occurring in public locations such as schools, restaurants, and airplanes. Educating patients about allergen avoidance strategies and managing allergic reactions while in unfamiliar or less controlled settings is essential (Table III). Because publicly accessible epinephrine is not generally available, patients at high risk of anaphylaxis should be prepared with their own epinephrine device at all times. Patients should be counseled that when the allergen trigger is food, the main route of exposure triggering anaphylaxis is ingestion. Food allergen exposure by contact or inhalation is unlikely to lead to severe reactions unless the allergen has been transferred to the mouth (eg, licking fingers)[19] or there is active aerosolization of the food allergy (eg, steam from boiled milk).[20]

Recommendations 16 to 18

Children spend a significant portion of their day in childcare centers and schools, so parents are frequently concerned about childcare center or school staff readiness to manage allergic reactions and anaphylaxis. Based on the 2021 Grading of Recommendations, Assessment, Development and Evaluation guideline for the prevention and management of allergic reactions in childcare centers and schools, approximately 10% of allergic reactions and anaphylaxis in children occurs in these settings.[21] This Grading of Recommendations, Assessment, Development, and Evaluation guideline conditionally recommends that childcare centers and schools implement staff training for allergy and anaphylaxis, because there is evidence that training and action plans may reduce the frequency of reactions and epinephrine use in students. Regarding allergen elimination, the guideline conditionally recommends against site-wide food

TABLE I. Practice parameter recommendations*

Recommendation	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 h after onset of symptoms). We suggest drawing a second (baseline) 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 hereditary α-tryptasemia in patients with elevated bST (≥8 ng/mL).	Conditional	Low
4	CBS	We suggest clinicians consider evaluation for mastocytosis, including a bone marrow biopsy, for adult patients with severe insect sting anaphylaxis or recurrent IA, particularly those with a predictive Red Espanola MAstocitosis† 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 National Institute of Allergy and Infectious Diseases/Food Allergy & Anaphylaxis Network‡ or World Allergy Organization§ 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 is not correlated with reaction severity.	Conditional	Very low
10	CBS	We suggest clinicians be aware that anaphylaxis is unlikely to be the initial reaction to a food or medication 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 0.15-mg EAI dose for infants/toddlers weighing <15 kg.	Conditional	Low
Anaphylaxis in community settings				
13	CBS	We recommend clinicians counsel patients at high-risk of anaphylaxis always to 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 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

(continued)

TABLE I. *(Continued)*

Recommendation	Method	Recommendation	Strength of recommendation	Certainty of evidence
19	CBS	We suggest clinicians counsel patients that although US regulations require disclosure of major allergens on labels of prepackaged foods, restaurants are not required to declare ingredients or provide allergy warnings for non-prepackaged foods.	Conditional	Very low
20	CBS	We suggest clinicians counsel patients on safe practices for dining outside 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 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 should be encouraged, if feasible.	Conditional	Very low
Epinephrine autoinjectors: when and how to prescribe				
23	CBS	We recommend clinicians routinely prescribe EAIs to patients at higher risk of anaphylaxis. When deciding whether to prescribe EAIs to lower-risk patients, we suggest that clinicians engage in a shared decision-making process that considers 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 one 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
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 emergency medical services 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 always to activate emergency medical services 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 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, common side effects, and the need for immediate evaluation and treatment when signs or symptoms of serious adverse events develop.	Strong	Low
28	CBS	We suggest that clinicians discuss the potential financial and psychosocial burdens of EAIs with patients while engaging in shared decision-making.	Conditional	Very low
29	CBS	When deciding which EAI to prescribe, we suggest that clinicians consider the 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

(continued)

TABLE I. *(Continued)*

Recommendation	Method	Recommendation	Strength of recommendation	Certainty of evidence
β-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 to patients with a history of insect sting anaphylaxis who are treated with BB or ACEI medication, with shared decision-making regarding the potential 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 minimal increased risk of severe anaphylactic reaction when receiving BB/ACEI medication and may consider continuing AIT and medications based on shared decision-making.	Conditional	Low
36	CBS	For planned procedures (eg, radiocontrast media, challenge/desensitization, and infusion) if the BB/ACEI medication cannot be safely interrupted, we suggest a 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 confirmed severe food allergy, those with mastocytosis or mast cell activation syndrome, or with recurrent IA) should 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 should not rely on serum tryptase levels alone for diagnostic assessment of the likelihood that a patient does or does not have a clonal mast cell disorder.	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 Red Espanola MAstocitosis score.	Conditional	Moderate
42	CBS	We suggest VIT be continued indefinitely in patients with mastocytosis and insect sting anaphylaxis owing to the increased risk of severe or fatal sting anaphylaxis if VIT is discontinued.	Conditional	Low

(continued)

TABLE I. *(Continued)*

Recommendation	Method	Recommendation	Strength of recommendation	Certainty of evidence
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 should be delayed after POA, unless repeat surgery cannot be postponed. If surgery with general anesthesia is needed sooner, testing should 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
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

ACEI, angiotensin-converting enzyme inhibitor; *alpha-gal*, galactose-alpha-1,3-galactose; *BB*, β-blocker; *bST*, baseline serum tryptase; *CBS*, consensus-based statement; *EAI*, epinephrine autoinjector; *GRADE*, Grading of Recommendations, Assessment, Development, and Evaluation; *IA*, idiopathic anaphylaxis; *POA*, perioperative anaphylaxis; *VIT*, venom immunotherapy.
*Reproduced from Golden et al.[1]
†Red Espanola MAstocitosis score.[2]
‡National Institute of Allergy and Infectious Diseases/Food Allergy & Anaphylaxis Network anaphylaxis criteria.[3]
§World Allergy Organization anaphylaxis criteria.[4]

specific prohibitions (food bans). However, allergen restrictions in limited locations may be appropriate when students lack the capacity to self-manage.

Childcare centers and schools may be the location of a student's first reaction, and reactions can occur in individuals who are not registered students (eg, school staff, visitors). Studies have shown that 15% to 31% of epinephrine use in these locations is for individuals who were not known by the school to have allergies. Therefore, the guideline suggests that childcare centers and schools have stock undesignated epinephrine devices available to treat any individual who experiences anaphylaxis onsite.[21]

Recommendations 19, 20, and 22

Food allergy reactions are often a concern in restaurants and on airplanes. However, there are limited studies examining anaphylaxis in these locations and little research on the effectiveness of strategies to mitigate risks. Labeling laws require the declaration of allergen ingredients in prepackaged foods, but ingredient lists and allergy warnings are not required for nonpackaged food such as restaurant and airplane meals. Patients are encouraged to disclose allergies to staff and recognize higher-risk situations for food allergen exposure (eg, buffets or shared dishes can lead to cross-contact).

Anaphylaxis can also occur in recreational public settings such as parks and other outdoor spaces. Insect sting-induced anaphylaxis, food-dependent exercise-induced anaphylaxis, and food-induced anaphylaxis during outdoor dining are examples of anaphylaxis occurring in these locations. There are few data concerning the frequency and circumstances of these anaphylaxis cases.

Although some state laws permit restaurants to stock undesignated epinephrine devices, and US airlines carry epinephrine vials and syringes on board, patients should be aware that epinephrine is generally unavailable in restaurants, airports, or other public locations. Therefore, patients should have their own epinephrine devices available at all times.

EPINEPHRINE

Recommendations 23 and 24

Epinephrine is the recommended first-line treatment for anaphylaxis. Clinicians should routinely prescribe epinephrine autoinjectors (EAIs) to patients at higher risk of anaphylaxis and engage those at lower risk in shared decision-making (SDM) that

TABLE II. Anaphylaxis in practice: key points (for clinicians)

Diagnosis:
Draw serum tryptase during an acute event (within 2 h of symptom onset) and at a separate time when the patient is otherwise in normal state of health, to help establish a diagnosis of anaphylaxis.
In patients presenting with idiopathic, recurrent, or severe (eg, hypotension and/or syncope) anaphylaxis, draw a baseline serum tryptase and consider hereditary α-tryptasemia, clonal mast cell disease, and galactose-alpha-1,3-galactose allergy.
Meeting diagnostic criteria many not always be required before the use of epinephrine, and receipt and response to epinephrine should not be used as diagnostic criteria of anaphylaxis.
Anaphylaxis in infants:
The current anaphylaxis criteria can be applied to infants and toddlers when determining whether an allergic reaction is likely to be anaphylaxis.
Reassure families that in infants, the initial reaction to an allergen trigger is unlikely to be anaphylaxis.
Recognize that signs and symptoms of anaphylaxis can manifest differently in infants and toddlers (eg, tongue thrusting or rubbing mouth as a sign of oral itching).
Anaphylaxis in the community:
Routinely educate patients on allergen avoidance measures and indications and technique for EAI use.
Counsel patients at high risk for anaphylaxis always to carry EAIs because epinephrine is often unavailable in community settings.
School management of anaphylaxis should include staff training.
Epinephrine for anaphylaxis:
Routinely prescribe EAI to patients at higher risk of anaphylaxis. Engage in SDM when determining whether to prescribe EAI to lower-risk patients.
Counsel patients to administer epinephrine at the first sign or symptom of suspected anaphylaxis. Also, counsel them on the proper carriage, storage, and use of the prescribed EAI as well as the common side effects and rare but serious adverse events to epinephrine.
Counsel patients always to activate emergency medical services after epinephrine use if the anaphylaxis is severe, it fails promptly to resolve completely or nearly completely, and/or it returns or worsens after the first dose of epinephrine.
In patients taking β-blocker/angiotensin-converting enzyme inhibitor medications:
The risk of avoiding VIT may exceed the risk of VIT treatment or of changing the medications. SDM is recommended. There is minimal increased risk on maintenance dose VIT.
Allergen immunotherapy may be considered with SDM. There is minimal increased risk on maintenance dose allergen immunotherapy.
Replacing β-blocker/angiotensin-converting enzyme inhibitor is preferable only if there is a safe and effective alternative.
Mast cell disorders:
Measure baseline serum tryptase in patients with severe sting anaphylaxis (particularly with hypotension or absence of urticaria), recurrent unexplained anaphylaxis, or suspected mastocytosis.
Do not rely on serum tryptase level alone to assess the likelihood of underlying mastocytosis.
Consider bone marrow biopsy for adult patients with severe sting anaphylaxis or recurrent IA, particularly with a predictive Red Espanola MAstocitosis score.
Perioperative anaphylaxis:
Measure serum tryptase during perioperative anaphylaxis (ideally within 30 min of reaction) and compare with baseline results to help establish the diagnosis of perioperative anaphylaxis.
Perform skin testing (percutaneous and intradermal) and/or *in vitro* specific IgE testing 4-6 wk after the event to all potential pharmacologic and nonpharmacologic agents used during the perioperative period, when possible.
Agents with positive testing should be avoided, and negative tests should be confirmed with challenge, whenever possible.

EAI, epinephrine autoinjector; *SDM*, shared decision-making; *VIT*, venom immunotherapy.

accounts for their individual risk factors, values and preferences, potential burdens of epinephrine prescription, and context-specific considerations (eg, emergency response times).[1] There are no validated risk-stratification algorithms to guide epinephrine prescription, but expert opinion suggests that the several factors may increase a patient's risk of requiring treatment with epinephrine (Table IV).[1] Older age and/or comorbidities (eg, uncontrolled asthma, cardiovascular disease, mast cell disorder) may also increase the risk of anaphylaxis or the severity of anaphylaxis (Table IV). Clinicians should prescribe at least two EAIs to patients with a history of anaphylaxis requiring multiple doses of epinephrine and/or biphasic anaphylaxis.[22-29]

Recommendations 12, 28, and 29

Clinicians should consider the dosage, needle length, affordability, accessibility, and patient treatment preferences when choosing among brands or formulations of EAI.[1] The standard recommended dosage of epinephrine for treating anaphylaxis is 0.01 mg/kg, up to a maximum of 0.3 mg for children and 0.5 mg for adults. The US Food and Drug Administration has approved several EAIs: 0.1 mg EAI for patients weighing 7.5 to 15 kg, 0.15 mg EAI for patients weighing 15 to 30 kg, and 0.3 mg EAI for patients weighing 30 kg or greater. Regulators in some other countries have also approved 0.5 mg EAI for patients weighing more than 60 kg. However, expert consensus supports switching to 0.3 mg EAI at 25 kg and 0.5 mg EAI at 45 kg (when available) to limit underdosing.[1,30] Clinical experience suggests it is safe to prescribe 0.1 or 0.15 mg EAI to infants and children weighing less than 15 kg.[31]

Recommendations 25, 27, and 30

Patient counseling should cover the proper storage, carriage, and use of prescribed EAIs, including the importance of administering epinephrine at the first sign or symptom of

TABLE III. Points and questions to consider for shared decision-making

Topics to consider when offering patient counseling
School
What is the school's management plan for food allergy and anaphylaxis?
What level of supervision is available for students?
What is developmentally appropriate for the students' age? Can they read ingredient labels? Can they self-recognize and inform staff of allergic reaction signs and symptoms? Can they self-carry the EAI? Can they self-administer the EAI?
Restaurants
What types of food are served at the restaurant?
How is food served (eg, prepackaged foods, table service, buffet, self-service, counter service)?
Airplane travel
What are sources of food during travel? Is it possible to have home-prepared food during the flight?
Topics to consider when using shared decision-making
Epinephrine autoinjector prescription
What are the patient's risk factors for requiring treatment with epinephrine (Table IV)?
Does the patient have factors that increase the risk of anaphylaxis in general, or severe anaphylaxis or biphasic anaphylaxis?
What are the burdens of EAI prescription or carriage for the patient?
Are certain brands or formulations of EAI easier for the patient to access or use (eg, owing to cost, insurance coverage, local availability, familiarity)?
Home management of anaphylaxis
Does the patient have a history of severe anaphylaxis treated with more than two doses of epinephrine, hospitalization, or intubation?
Does the patient have access to at least two EAIs and someone to provide help if needed?
Does the patient understand signs and symptoms that warrant epinephrine use?
Does the patient have an anaphylaxis treatment plan available?
Does the patient feel comfortable with home management?
Does the patient have good adherence to previous treatment recommendations and plans?
β-**blocker**/angiotensin-converting enzyme inhibitor
Has there been a discussion among the allergist, prescribing physician, and patient regarding whether there is an alternative medication that is equally safe and effective?
What are the risks and benefits of the allergy treatment or procedure (allergen immunotherapy, venom immunotherapy, or drug or food challenges)?
Perioperative anaphylaxis
Has there been a discussion between the allergist and patient as to the risks and benefits of skin testing and/or challenges to perioperative agents that may have been responsible for the previous anaphylaxis?
Has there been a discussion among the allergist, surgeon, and patient as to the advisability of delaying repeat surgery?
Before a planned surgery and after any diagnostic testing or challenges, if completed, has there been a discussion among the allergist, surgeon, anesthesiologist, and patient as to the risk of a reaction to the selected perioperative pharmacologic or nonpharmacologic agents?

EAI, epinephrine autoinjector.

suspected anaphylaxis.[1] There is no evidence that preemptively administering epinephrine to asymptomatic patients prevents anaphylaxis after exposure to a potential trigger.[32] Clinicians should discuss potential barriers to treatment adherence, regularly review the essentials of EAIs, and encourage patients to practice with EAI trainer devices.[33] They should counsel patients about the common side effects of epinephrine as well the potential signs and symptoms of rare but serious adverse events that require immediate evaluation and treatment. The risk of serious adverse reactions to intramuscular epinephrine is low and should not pose barriers to EAI prescription or use.[34-36]

Recommendation 26

Clinicians should counsel patients always to activate emergency medical services after epinephrine administration when the anaphylaxis is severe, symptoms do not promptly resolve completely or nearly completely, and/or symptoms return or worsen after the first dose of epinephrine.[1,37,38] Immediate activation of emergency medical services after epinephrine use may not be necessary if the patient experiences a prompt, complete or nearly complete, and durable response to treatment and has additional doses of epinephrine available. In such cases, home management of anaphylaxis may be considered (Table III). When developing an anaphylaxis management plan, clinicians and patients should engage in SDM that considers their risk factors for severe and biphasic anaphylaxis, access to epinephrine and medical services, and capacity to administer EAI effectively and gauge treatment response (Table III).

β-BLOCKERS AND ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Historical reports suggested that β-blockers (BBs) and angiotensin-converting enzyme inhibitors (ACEIs) increase the risk and severity of anaphylaxis, which is of special concern when there is unavoidable allergen exposure and/or frequent anaphylactic reactions. The historical studies were generally small and included nonselective BBs, and they usually failed to adjust for underlying cardiovascular comorbidities.[39-43] Subsequent individual studies and systematic reviews have not found evidence that these medications are associated with more frequent anaphylaxis, and they have found conflicting evidence about whether they are associated with more severe anaphylaxis.[40,43,44] A case-controlled study showed that the higher frequency of

TABLE IV. Factors that may increase patient's risk of requiring treatment with epinephrine

Frequent or occupational allergen exposure
History of systemic allergic reaction or anaphylaxis to causative food
Venom allergy with honey bee as trigger, elevated baseline serum tryptase, history of anaphylaxis not treated with venom immunotherapy, and/or prior systemic allergic reaction to venom immunotherapy
Aeroallergy with history of systemic allergic reaction to aeroallergen immunotherapy
History of idiopathic anaphylaxis, exercise-induced anaphylaxis, or cold-induced urticaria
Older age
Comorbidities (eg, uncontrolled asthma, cardiovascular disease, mast cell disorder)

severe cardiovascular anaphylaxis in patients taking BBs and/or ACEIs (BB/ACEIs) was correlated with preexisting cardiovascular disease.[45] Furthermore, a prospective observational study of insect venom anaphylaxis found that BB/ACEI use was not associated with the increased frequency or severity of anaphylaxis to live stings, venom immunotherapy (VIT), or stings during VIT.[46] There is no evidence that patients receiving BB who experience anaphylaxis require more doses of epinephrine to treat the reaction.[41] Selective β-1 BBs may pose less risk than nonselective BBs.[43,47,48] In all situations, it would be appropriate to consider changing the BB/ACEI medication if there is an alternative medication that is equally effective and equally safe. There is an important role for SDM in many of the clinical scenarios discussed subsequently (Table III). This discussion should include all appropriate options (eg, alternative medication) as well as the risks and benefits of the treatment or procedure.

Recommendations 31 to 33

For VIT, the major risk factor for severe anaphylaxis (aside from mast cell disorders) is the presence of underlying cardiovascular disease rather than the use of BB/ACEIs to treat this disease.[40,45,46,49-53] For most patients with venom-induced anaphylaxis, the benefit of continuing BB/ACEI to maintain control of the cardiovascular disease will outweigh the potential risk of increased anaphylaxis frequency and severity regardless of whether the patient chooses for or against the initiation or continuation of VIT.

Recommendations 34 and 35

The use of BB/ACEIs during sublingual aeroallergen immunotherapy is not associated with the increased frequency or severity of systemic reactions.[39,54] The use of BB/ACEIs during inhalant subcutaneous immunotherapy has not been found to increase the frequency of systemic reactions, but it may increase their severity.[55] The absolute risk remains less than 0.2%, even without adjustment for underlying cardiovascular disease.[1,56] The decision to initiate or continue subcutaneous immunotherapy should be made through SDM.[1]

Recommendations 36 and 37

For planned high-risk procedures (eg, radiocontrast media use, drug challenge and desensitization, oral food challenge, and intravenous immunoglobulin infusions), there are limited and often conflicting data on the effect of BB/ACEIs on the risk of severe anaphylaxis for the procedure, and there may be significant risk in discontinuing the medication, emphasizing the value of SDM.[1,43,57]

Patients with recurrent and/or unexpected anaphylaxis (eg, IA, severe food allergy, mastocytosis) who are taking BB/ACEIs may be at increased risk of severe anaphylaxis, but there are inadequate data with which to reach a firm conclusion, supporting the need for SDM.[1] Patients with severe food allergy who are concurrently receiving BB/ACEIs have been found to have an increased risk of severe anaphylaxis, but the confounding factor of increased age in the affected patients is likely to be the most significant risk factor.[58] Counseling for patients in this high-risk group should include both the consideration of alternative medications (eg, selective vs nonselective BBs, angiotensin receptor blockers vs ACEIs) and anaphylaxis preparedness (eg, immediate access to EAIs).

MAST CELL DISORDERS

Given the association of mast cell disorders with anaphylaxis, it is important to consider mast cell disorders in the evaluation of patients with anaphylaxis.[1] Early observations noted the association of CMD and/or elevated bST with severe or fatal anaphylaxis, especially with reactions to insect stings, including treatment failure or relapse after completing a course of VIT (in some cases fatal).[59-64] Elevated bST may be found in up to 20% of patients with severe anaphylaxis, and CMD has been reported in 14% of patients with IA[65] and more than 20% of patients with severe sting anaphylaxis.[66,67]

Mastocytosis is the most common CMD and is associated with both the higher frequency and greater severity of anaphylaxis. Insect sting allergy is the most common cause and IA is the second most common one.[61,68,69] The diagnosis of mastocytosis according to World Health Organization criteria requires bone marrow biopsy, but an initial investigation can include serum tryptase and blood testing for D816V c-KIT mutation. In some patients with mastocytosis, the bST may be normal. Although the accuracy of blood testing for c-KIT mutation is improved through the use of the high-sensitivity PCR assay, it is still not as sensitive as bone marrow biopsy.[68] Patients with mastocytosis and insect sting anaphylaxis often have a unique phenotype with prominent hypotension and the absence of urticaria, the absence of cutaneous mastocytosis, bST that can be normal or elevated, and a low mast cell burden (although fulfilling the criteria for mastocytosis in bone marrow).[70,71]

These observations have been used to create scoring systems to identify patients with anaphylaxis who should be evaluated for mastocytosis with bST testing and bone marrow biopsy. The Red Espanola MAstocitosis score described by the Spanish Mastocytosis Network has been validated in additional studies.[12,68] The National Institutes of Health Idiopathic Clonal Anaphylaxis Score has a similar predictive value, but that population did not include venom anaphylaxis.[65]

Recommendations 38 to 42

Based on these observations, bST should be measured in all patients with anaphylaxis, particularly those with hypotension and/or the absence of urticaria and those with insect sting or IA.[1] Clinicians should not rely on bST alone to assess the possibility of CMD, and should order a bone marrow biopsy and comprehensive immunopathologic examination when CMD is suspected. Although the normal range of bST is 1 to 15 ng/

mL,[72] in the context of anaphylaxis, any level greater than 8 ng/mL may warrant investigation to detect HαT or CMD, and bone marrow biopsy may be necessary even when tryptase is less than 8 ng/mL to detect CMD.[1] Both conditions are important because they are overrepresented in patients with anaphylaxis (compared with the general population) and are associated with severe anaphylaxis.[11] For patients with CMD who are receiving VIT, it is recommended to continue treatment indefinitely because of the risk of fatal sting reaction if it is stopped. Although it is unclear whether HαT definitely increases the risk of reaction severity in patients with venom allergy, it would be reasonable also to consider lifelong therapy for patients with HαT who are receiving VIT.

Treatment for patients with mastocytosis usually targets those with uncontrolled symptoms and an increasing mast cell burden. In the case of anaphylaxis of known or unknown cause, patients with mastocytosis are at increased risk for more frequent and severe reactions. Individuals with recurrent episodes requiring emergency treatment would benefit from therapy to reduce the frequency and/or severity of anaphylaxis. There is some evidence that omalizumab can reduce the risk of anaphylaxis during immunotherapy and in patients with IA, and it is now approved by the Food and Drug Administration for patients with multiple food allergies.[73-75] There is experimental evidence that Bruton tyrosine kinase inhibitors can reduce the anaphylactic response, and they have been shown to be efficacious in controlling chronic spontaneous urticaria.[76,77]

PERIOPERATIVE ANAPHYLAXIS

Perioperative anaphylaxis (POA) occurs at an approximate rate of 15.3 events/100,000 cases. Reported risk factors include male sex, emergency surgery, history of hypertension or other cardiovascular disease, obesity, and BB exposure.[78] The most common culprits are antibiotics and neuromuscular blocking agents, although this may vary geographically. When a reaction occurs during an operation, a serum tryptase level drawn within 30 minutes of the reaction has been shown to be helpful in determining whether POA has occurred. Most data use the 20% + 2 rule discussed earlier.[79]

Recommendations 43 to 47

When POA is suspected, regardless of whether tryptase was acutely elevated, percutaneous and intradermal skin testing and/or *in vitro* specific IgE testing should be done to all potential pharmacologic and nonpharmacologic culprits used during the perioperative period, although the validity of this testing is unknown for most perioperative agents. Although antibiotics and neuromuscular blocking agents are the most common culprits, testing only to these will miss many culprits. The practice parameter provides a table with nonirritating skin testing concentrations that can be used for most possible culprits. Testing to all culprits may not be feasible in many areas, especially in community practices where access to medications may be limited; thus, referral to another center should be considered when necessary. Testing should ideally be delayed 4 to 6 weeks after the POA event, owing to a possible refractory period that has been reported to lead to false-negative testing.[80] However, if repeat surgery cannot be delayed, an SDM approach should be taken with the patient and care team (eg, anesthesiologist, surgeon) to determine the risks and benefits of proceeding with anesthesia and which agents to use for anesthesia (Table III).

Once testing is conducted as earlier, negative tests should ideally be confirmed with a challenge, but that repeat anesthesia may proceed in the context of SDM (Table III). The challenge can be conducted before a future operation by anesthesia, and if desired, a 10% test dose can be given before the challenge if there is concern. When a challenge is not feasible, agents structurally unrelated to any agents used in the original POA event can be used, assuming the structurally unrelated agents are equally efficacious.

Recommendation 48

There is not enough evidence to recommend pretreatment before returning to the operating room in patients with negative testing.

CONCLUSIONS

The 2023 anaphylaxis practice parameter update aims to provide guidance on clinically important questions pertaining to the diagnosis and management of anaphylaxis. Evolving evidence has advanced our understanding of anaphylaxis in the focus areas discussed in the practice parameter. However, gaps in knowledge remain because much of the available evidence is low to very low certainty and is derived from observational studies, case series, and expert opinion. Continued work is needed to develop validated diagnostic criteria for anaphylaxis, which in turn will support research efforts to identify biomarkers and inform optimal strategies for acute and long-term management of patients at risk for anaphylaxis.

REFERENCES

1. Golden DBK, Wang J, Waserman S, Akin C, Campbell RL, Ellis AK, et al. Anaphylaxis: a 2023 practice parameter update. Ann Allergy Asthma Immunol 2024;132:124-76.
2. Alvarez-Twose I, González-de-Olano D, Sánchez-Muñoz L, Matito A, Jara-Acevedo M, Teodosio C, et al. Validation of the REMA score for predicting mast cell clonality and systemic mastocytosis in patients with systemic mast cell activation symptoms. Int Arch Allergy Immunol 2012;157:275-80.
3. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report–Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391-7.
4. Cardona V, Ansotegui IJ, Ebisawa M, El-Gamal Y, Fernandez Rivas M, Fineman S, et al. World allergy organization anaphylaxis guidance 2020. World Allergy Organ J 2020;13:100472.
5. Muraro A, Roberts G, Worm M, Bilò MB, Brockow K, Fernández Rivas M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy 2014;69:1026-45.
6. Lieberman JA, Bingemann TA, Wang J. Diagnostic challenges in anaphylaxis. J Allergy Clin Immunol Pract 2020;8:1177-84.
7. Valent P, Akin C, Arock M, Brockow K, Butterfield JH, Carter MC, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. Int Arch Allergy Immunol 2012;157:215-25.
8. Mateja A, Wang Q, Chovanec J, Kim J, Wilson KJ, Schwartz LB, et al. Defining baseline variability of serum tryptase levels improves accuracy in identifying anaphylaxis. J Allergy Clin Immunol 2022;149:1010-1017.e10.
9. Lyons JJ, Greiner G, Hoermann G, Metcalfe DD. Incorporating tryptase genotyping into the workup and diagnosis of mast cell diseases and reactions. J Allergy Clin Immunol Pract 2022;10:1964-73.
10. Giannetti MP, Weller E, Bormans C, Novak P, Hamilton MJ, Castells M. Hereditary alpha-tryptasemia in 101 patients with mast cell activation-related symptomatology including anaphylaxis. Ann Allergy Asthma Immunol 2021;126:655-60.
11. Lyons JJ, Chovanec J, O'Connell MP, Liu Y, Selb J, Zanotti R, et al. Heritable risk for severe anaphylaxis associated with increased alpha-tryptase-encoding germline copy number at TPSAB1. J Allergy Clin Immunol 2021;147:622-32.

12. Alvarez-Twose I, González de Olano D, Sánchez-Muñoz L, Matito A, Esteban-López MI, Vega A, et al. Clinical, biological, and molecular characteristics of clonal mast cell disorders presenting with systemic mast cell activation symptoms. J Allergy Clin Immunol 2010;125:1269-1278.e2.
13. Pattanaik D, Lieberman P, Lieberman J, Pongdee T, Keene AT. The changing face of anaphylaxis in adults and adolescents. Ann Allergy Asthma Immunol 2018;121:594-7.
14. Soriano VX, Peters RL, Ponsonby AL, Dharmage SC, Perrett KP, Field MJ, et al. Earlier ingestion of peanut after changes to infant feeding guidelines: the EarlyNuts study. J Allergy Clin Immunol 2019;144:1327-1335.e5.
15. Jeong K, Ye YM, Kim SH, Kim KW, Kim JH, Kwon JW, et al. A multicenter anaphylaxis registry in Korea: Clinical characteristics and acute treatment details from infants to older adults. World Allergy Organ J 2020;13:100449.
16. Robinson LB, Arroyo AC, Faridi MK, Rudders S, Camargo CA Jr. Trends in US emergency department visits for anaphylaxis among infants and toddlers: 2006-2015. J Allergy Clin Immunol Pract 2021;9:1931-1938.e2.
17. Robinson LB, Arroyo AC, Faridi MK, Rudders SA, Camargo CA Jr. Trends in US hospitalizations for anaphylaxis among infants and toddlers: 2006-2015. Ann Allergy Asthma Immunol 2021;126:168-174.e3.
18. Pistiner M, Mendez-Reyes JE, Eftekhari S, Carver M, Lieberman J, Wang J, et al. Caregiver-reported presentation of severe food-induced allergic reactions in infants and toddlers. J Allergy Clin Immunol Pract 2021;9:311-320.e2.
19. Simonte SJ, Ma S, Mofidi S, Sicherer SH. Relevance of casual contact with peanut butter in children with peanut allergy. J Allergy Clin Immunol 2003;112:180-2.
20. Roberts G, Golder N, Lack G. Bronchial challenges with aerosolized food in asthmatic, food-allergic children. Allergy 2002;57:713-7.
21. Waserman S, Cruickshank H, Hildebrand KJ, Mack D, Bantock L, Bingemann T, et al. Prevention and management of allergic reactions to food in child care centers and schools: practice guidelines. J Allergy Clin Immunol 2021;147:1561-78.
22. Turner PJ, Jerschow E, Umasunthar T, Lin R, Campbell DE, Boyle RJ. Fatal anaphylaxis: mortality rate and risk factors. J Allergy Clin Immunol Pract 2017;5:1169-78.
23. Turner PJ, Gowland MH, Sharma V, Ierodiakonou D, Harper N, Garcez T, et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992-2012. J Allergy Clin Immunol 2015;135:956-963.e1.
24. De Feo G, Parente R, Cardamone C, Bucci T, Guerritore L, Triggiani M. Risk factors and cofactors for severe anaphylaxis. Curr Treat Options Allergy 2018;5:204-11.
25. Worm M, Francuzik W, Renaudin JM, Bilo MB, Cardona V, Scherer Hofmeier K, et al. Factors increasing the risk for a severe reaction in anaphylaxis: an analysis of data from The European Anaphylaxis Registry. Allergy 2018;73:1322-30.
26. Anagnostou A, Sharma V, Herbert L, Turner PJ. Fatal food anaphylaxis: distinguishing fact from fiction. J Allergy Clin Immunol Pract 2022;10:11-7.
27. Motosue MS, Bellolio MF, Van Houten HK, Shah ND, Campbell RL. Risk factors for severe anaphylaxis in the United States. Ann Allergy Asthma Immunol 2017;119:356-361.e2.
28. Roberts G, Allen K, Ballmer-Weber B, Clark A, Crevel R, Dunn Galvin A, et al. Identifying and managing patients at risk of severe allergic reactions to food: report from two iFAAM workshops. Clin Exp Allergy 2019;49:1558-66.
29. Tan-Lim CSC, Castor MAR, Recto MST, Casis-Hao RJ, Nano ALM. Predictors of serious outcomes among patients with anaphylaxis seen in the Philippine national tertiary hospital. Asia Pac Allergy 2021;11:e8.
30. Brown JC. Epinephrine, auto-injectors, and anaphylaxis: challenges of dose, depth, and device. Ann Allergy Asthma Immunol 2018;121:53-60.
31. Shaker MS, Wallace DV, Golden DBK, Oppenheimer J, Bernstein JA, Campbell RL, et al. Anaphylaxis: a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. J Allergy Clin Immunol 2020;145:1082. 23.
32. Shaker M, Greenhawt M. The health and economic outcomes of peanut allergy management practices. J Allergy Clin Immunol Pract 2018;6:2073-80.
33. Trujillo J, Cronin C. Benefit of educational intervention on autoinjector technique for caregivers and paediatric patients with food allergies: a literature review. Allergol Immunopathol (Madr) 2022;50:100-13.
34. Campbell RL, Bellolio MF, Knutson BD, Bellamkonda VR, Fedko MG, Nestler DM, et al. Epinephrine in anaphylaxis: higher risk of cardiovascular complications and overdose after administration of intravenous bolus epinephrine compared with intramuscular epinephrine. J Allergy Clin Immunol Pract 2015;3:76-80.
35. Cardona V, Ferré-Ybarz L, Guilarte M, Moreno-Pérez N, Gómez-Galán C, Alcoceba-Borràs E, et al. Safety of adrenaline use in anaphylaxis: a multicentre register. Int Arch Allergy Immunol 2017;173:171-7.
36. Shaker M, Toy D, Lindholm C, Low J, Reigh E, Greenhawt M. Summary and simulation of reported adverse events from epinephrine autoinjectors and a review of the literature. J Allergy Clin Immunol Pract 2018;6:2143-2145.e4.
37. Shaker M, Kanaoka T, Feenan L, Greenhawt M. An economic evaluation of immediate vs non-immediate activation of emergency medical services after epinephrine use for peanut-induced anaphylaxis. Ann Allergy Asthma Immunol 2019;122:79-85.
38. Casale TB, Wang J, Oppenheimer J, Nowak-Wegrzyn A. Acute at-home management of anaphylaxis: 911: what is the emergency? J Allergy Clin Immunol Pract 2022;10:2274-9.
39. Smith DM, Coop CA, Freeman TM. Beta-Blockers and angiotensin-converting enzyme inhibitors with sublingual immunotherapy: are risks related to individual product safety profile? Curr Opin Allergy Clin Immunol 2020;20:401-6.
40. Tejedor-Alonso MA, Farias-Aquino E, Perez-Fernandez E, Grifol-Clar E, Moro-Moro M, Rosado-Ingelmo A. Relationship between anaphylaxis and use of beta-blockers and angiotensin-converting enzyme inhibitors: a systematic review and meta-analysis of observational studies. J Allergy Clin Immunol Pract 2019;7:879-897.e5.
41. White JL, Greger KC, Lee S, Kahoud RJ, Li JT, Lohse CM, et al. Patients taking beta-blockers do not require increased doses of epinephrine for anaphylaxis. J Allergy Clin Immunol Pract 2018;6:1553-1558.e1.
42. Miller MM, Miller MM. Beta-blockers and anaphylaxis: are the risks overstated? J Allergy Clin Immunol 2005;116:931-3. author reply 3-6.
43. Smith MA, Newton LP, Barcena Blanch MA, Cuervo-Pardo L, Cho L, Newton D, et al. Risk for anaphylactic reaction from cardiac catheterization in patients receiving beta-adrenergic blockers or angiotensin-converting enzyme-inhibitors. J Allergy Clin Immunol Pract 2020;8:1900-5.
44. Carlson GS, Wong PH, White KM, Quinn JM. Evaluation of angiotensin-converting enzyme inhibitor and angiotensin receptor blocker therapy in immunotherapy-associated systemic reactions. J Allergy Clin Immunol Pract 2017;5:1430-2.
45. Francuzik W, Rueff F, Bauer A, Bilo MB, Cardona V, Christoff G, et al. Phenotype and risk factors of venom-induced anaphylaxis: a case-control study of the European Anaphylaxis Registry. J Allergy Clin Immunol 2021;147:653-662.e9.
46. Sturm GJ, Herzog SA, Aberer W, Alfaya Arias T, Antolin-Amerigo D, Bonadonna P, et al. beta-blockers and ACE inhibitors are not a risk factor for severe systemic sting reactions and adverse events during venom immunotherapy. Allergy 2021;76:2166-76.
47. Toh S, Reichman ME, Houstoun M, Ross Southworth M, Ding X, Hernandez AF, et al. Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. Arch Intern Med 2012;172:1582-9.
48. Nassiri M, Babina M, Dolle S, Edenharter G, Rueff F, Worm M. Ramipril and metoprolol intake aggravate human and murine anaphylaxis: evidence for direct mast cell priming. J Allergy Clin Immunol 2015;135:491-9.
49. Muller UR, Haeberli G. Use of beta-blockers during immunotherapy for Hymenoptera venom allergy. J Allergy Clin Immunol 2005;115:606-10.
50. Rueff F, Vos B, Oude Elberink J, Bender A, Chatelain R, Dugas-Breit S, et al. Predictors of clinical effectiveness of Hymenoptera venom immunotherapy. Clin Exp Allergy 2014;44:736-46.
51. Rueff F, Przybilla B, Bilo MB, Muller U, Scheipl F, Aberer W, et al. Predictors of side effects during the buildup phase of venom immunotherapy for Hymenoptera venom allergy: the importance of baseline serum tryptase. J Allergy Clin Immunol 2010;126:105-111.e5.
52. Stoevesandt J, Hosp C, Kerstan A, Trautmann A. Hymenoptera venom immunotherapy while maintaining cardiovascular medication: safe and effective. Ann Allergy Asthma Immunol 2015;114:411-6.
53. Stoevesandt J, Hain J, Stolze I, Kerstan A, Trautmann A. Angiotensin-converting enzyme inhibitors do not impair the safety of Hymenoptera venom immunotherapy build-up phase. Clin Exp Allergy 2014;44:747-55.
54. Greenhawt M, Oppenheimer J, Nelson M, Nelson H, Lockey R, Lieberman P, et al. Sublingual immunotherapy: a focused allergen immunotherapy practice parameter update. Ann Allergy Asthma Immunol 2017;118:276-282.e2.
55. Dhamija Y, Epstein TEG, Bernstein DI. Systemic allergic reactions and anaphylaxis associated with allergen immunotherapy. Immunol Allergy Clin North Am 2022;42:105-19.
56. Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. J Allergy Clin Immunol 2010;125:569-574.e1-7.
57. Lang DM, Alpern MB, Visintainer PF, Smith ST. Elevated risk of anaphylactoid reaction from radiographic contrast media is associated with

both beta-blocker exposure and cardiovascular disorders. Arch Intern Med 1993;153:2033-40.
58. Turner PJ, Arasi S, Ballmer-Weber B, Baseggio Conrado A, Deschildre A, Gerdts J, et al. Risk factors for severe reactions in food allergy: rapid evidence review with meta-analysis. Allergy 2022;77:2634-52.
59. Haeberli G, Bronnimann M, Hunziker T, Muller U. Elevated basal serum tryptase and hymenoptera venom allergy: relation to severity of sting reactions and to safety and efficacy of venom immunotherapy. Clin Exp Allergy 2003;33:1216-20.
60. Muller UR. Elevated baseline serum tryptase, mastocytosis and anaphylaxis. Clin Exp Allergy 2009;39:620-2.
61. Niedoszytko M, Bonadonna P, Oude Elberink JN, Golden DB. Epidemiology, diagnosis, and treatment of Hymenoptera venom allergy in mastocytosis patients. Immunol Allergy Clin North Am 2014;34:365-81.
62. Rueff F, Przybilla B, Bilo MB, Muller U, Scheipl F, Aberer W, et al. Predictors of severe systemic anaphylactic reactions in patients with Hymenoptera venom allergy: importance of baseline serum tryptase-a study of the European Academy of Allergology and Clinical Immunology Interest Group on Insect Venom Hypersensitivity. J Allergy Clin Immunol 2009;124:1047-54.
63. Bonadonna P, Scaffidi L. Hymenoptera anaphylaxis as a clonal mast cell disorder. Immunol Allergy Clin North Am 2018;38:455-68.
64. Golden DB, Demain J, Freeman T, Graft D, Tankersley M, Tracy J, et al. Stinging insect hypersensitivity: a practice parameter update 2016. Ann Allergy Asthma Immunol 2017;118:28-54.
65. Carter MC, Desai A, Komarow HD, Bai Y, Clayton ST, Clark AS, et al. A distinct biomolecular profile identifies monoclonal mast cell disorders in patients with idiopathic anaphylaxis. J Allergy Clin Immunol 2018;141:180-188.e3.
66. Selb J, Rijavec M, Erzen R, Zidarn M, Kopac P, Skerget M, et al. Routine KIT p.D816V screening identifies clonal mast cell disease in patients with Hymenoptera allergy regularly missed using baseline tryptase levels alone. J Allergy Clin Immunol 2021;148:621-626.e7.
67. Vazquez-Revuelta P, Gonzalez-de-Olano D. Prevalence of clonal mast cell disorders in patients presenting with Hymenoptera venom anaphylaxis might be higher than expected. J Investig Allergol Clin Immunol 2018;28:193-4.
68. Gulen T, Hagglund H, Dahlen B, Nilsson G. High prevalence of anaphylaxis in patients with systemic mastocytosis - a single-centre experience. Clin Exp Allergy 2014;44:121-9.
69. Brockow K, Jofer C, Behrendt H, Ring J. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. Allergy 2008;63:226-32.
70. Alvarez-Twose I, Zanotti R, Gonzalez-de-Olano D, Bonadonna P, Vega A, Matito A, et al. Nonaggressive systemic mastocytosis (SM) without skin lesions associated with insect-induced anaphylaxis shows unique features versus other indolent SM. J Allergy Clin Immunol 2014;133:520-8.
71. Zanotti R, Bonadonna P, Bonifacio M, Artuso A, Schena D, Rossini M, et al. Isolated bone marrow mastocytosis: an underestimated subvariant of indolent systemic mastocytosis. Haematologica 2011;96:482-4.
72. Valent P, Hoermann G, Bonadonna P, Hartmann K, Sperr WR, Broesby-Olsen S, et al. The normal range of baseline tryptase should be 1 to 15 ng/mL and covers healthy individuals with HαT. J Allergy Clin Immunol Pract 2023;11:3010-20.
73. Dantzer JA, Wood RA. Update on omalizumab in allergen immunotherapy. Curr Opin Allergy Clin Immunol 2021;21:559-68.
74. Kaminsky LW, Aukstuolis K, Petroni DH, Al-Shaikhly T. Use of omalizumab for management of idiopathic anaphylaxis: a systematic review and retrospective case series. Ann Allergy Asthma Immunol 2021;127:481-7.
75. Wood RA, Togias A, Sicherer SH, Shreffler WG, Kim EH, Jones SM, et al. Omalizumab for the treatment of multiple food allergies. N Engl J Med 2024;390:889-99.
76. Suresh RV, Dunnam C, Vaidya D, Wood RA, Bochner BS, MacGlashan DW Jr, et al. A phase II study of Bruton's tyrosine kinase inhibition for the prevention of anaphylaxis. J Clin Invest 2023;133:e172335.
77. Maurer M, Berger W, Gimenez-Arnau A, Hayama K, Jain V, Reich A, et al. Remibrutinib, a novel BTK inhibitor, demonstrates promising efficacy and safety in chronic spontaneous urticaria. J Allergy Clin Immunol 2022;150:1498-1506.e2.
78. Gonzalez-Estrada A, Carrillo-Martin I, Renew JR, Rank MA, Campbell RL, Volcheck GW. Incidence of and risk factors for perioperative or periprocedural anaphylaxis in the United States from 2005 to 2014. Ann Allergy Asthma Immunol 2021;126:180-186.e3.
79. Vitte J, Amadei L, Gouitaa M, Mezouar S, Zieleskiewicz L, Albanese J, et al. Paired acute-baseline serum tryptase levels in perioperative anaphylaxis: an observational study. Allergy 2019;74:1157-65.
80. Goldberg A, Confino-Cohen R. Timing of venom skin tests and IgE determinations after insect sting anaphylaxis. J Allergy Clin Immunol 1997;100:182-4.