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Practice Parameter

Anaphylaxis—a practice parameter update 2015

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Disclosures: The following is a summary of interests disclosed on work group members' Conflict of Interest Disclosure Statements (not including information concerning family member interests). Completed Conflict of Interest Disclosure Statements are available upon request. David Bernstein, MD, is on the advisory boards of Teva and Circassion; is on the board of the American Board of Allergy and Immunology; is a consultant for Proctor & Gamble, Science Strategies, Guidepoint Federal, and Merck; provides legal support for Fowler, Whited, & Barrett; is speaker for Merck; and has received financial support from the Centers for Disease Control and Prevention and the National Institute for Occupational Safety and Health (principal investigator) and Teva, Merck, Glaxo, Pfizer, Genentech, Novartis, Astra Zeneca, Amgon, Savoy, and Cephalon. Jonathan Bernstein, MD, has consulted for and received honorarium and gifts from Sanofi Aventis; served as consultant, speaker and researcher for Dyax, Shire, CSL Behring, ViroPharma, and research for Pharming, is the editor of the *Journal of Asthma;* serves on the AAAAI Board of Directors; is a committee member of the ACAAI, and is chair of the Allergists for Israel. Anne Ellis, MD, is s speaker for Pfizer Canada, Merck, and Astra; is on the advisory board of Palladin Labs; received a research grant from Circassia Ltd; and is on the Drug, Allergy & Anaphylaxis Committee of the ACAAI. David B.K. Golden, MD, is a consultant for Sanofi and GlaxoSmithKline, speaker for Genentech, and has received financial support from Siemens for a clinical trial. Paul Greenberger, MD, has consulted for Mylan (Day) and is a committee member of the Food and Drug Administration Pulmonary Allergy Drugs Advisory Committee. Kevin J. Kelly, MD, received research grants from Targacept, Merck Schering, Schering, Chiltern, and Glaxo; has consulted for the University of North Carolina; and is a leadership board member of the American Lung Association of Wisconsin. Steven Kemp, MD, is a committee member, assembly member, and speaker for the AAAAI; is an editorial board member and committee member of the ACAAI; and is on the board of directors for the American Board of Allergy & Immunology. David Khan, MD, is a speaker for Baxter and Genentech. Dennis Ledford, MD, is a speaker for the South Carolina Allergy & Immunology Society and Meda Pharmaceutical; has received research grants from Teva, Forest, Genentech, Merck, and ViroPharma; has consulted for Shook Hardy Bacon, Saieva and Stine, and Genentech; is on the advisory board of AstraZeneca. Jay Lieberman, MD, reports no conflicts. Philip Lieberman, MD, consults for Sanofi Aventis, Neyian, Merck, Genentech, Teva, Meda, and the Asthma and Allergy Foundation of America; serves on the advisory boards of Sanofi Aventis, Neyian, Merck, Teva, and Meda; and served as speaker for Neyina, Teva, and Meda. Dean Metcalfe, MD, reports no conflicts. Anna Nowak-Wegrzyn, MD, is on the advisory boards of Merck and Nutricia; has served as speaker for Thermofisher Scientific; and received a research grant from Nutucia. Scott Sicherer, MD, consults for Novartis; edits and receives honorarium from the *Journal of Allergy and Clinical Immunology* and is associate editor of the *Journal of Allergy and Clinical Immunology In Practice;* serves as speaker for and receives honorarium from the American Academy of Pediatrics; received honorarium from the American Board of Allergy and Immunology; is on the advisory board of Sanofi; edits and contributes to *UpToDate;* consults for the Food Allergy Initiative; received research grants from the National Institute of Allergy and Infectious Diseases, National Institutes of Health; is on the executive committee of the American Academy of Pediatrics; and is a medical advisor for the Food Allergy and Anaphylaxis Network and Food Allergy Research and Education. Dana Wallace, MD, is on the advisory board of Sanofi, Sunovion, and Mylan; serves as speaker for Sunovion, Teva, and Meda; and is on the board of directors of the World Allergy Organization. The Joint Task Force recognizes that experts in a field are likely to have interests that could come into conflict with development a completely unbiased and objective practice parameter. To take advantage of that expertise, a process has been developed to prevent potential conflicts from influencing the final document in a negative way. At the workgroup level, members who have a potential conflict of interest do not participate in discussions concerning topics related to the potential conflict; or if they do write a section on that topic, the workgroup completely rewrites it without their involvement to remove potential bias. In addition, the entire document is reviewed by the Joint Task Force and any apparent bias is removed at that level. Moreover, the practice

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Classification of Recommendations and Evidence

Frequently, there can be a separation between the strength of recommendation and quality of evidence.

Recommendation Rating Scale

Statement	Definition	Implication
Strong recommendation	A strong recommendation means the benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (grade A or B)*. In some clearly identified circumstances, strong recommendations might be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Recommendation	A recommendation means the benefits exceed the harms (or that the harms clearly exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong (grade B or C)*. In some clearly identified circumstances, recommendations might be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms.	Clinicians also should generally follow a recommendation but should remain alert to new information and sensitive to patient values and preferences.
Weak	An option means that the quality of evidence that exists is suspect (grade D)* or that well-done studies (grade A, B, or C)* show little clear advantage to one approach vs another.	Clinicians should be flexible in their decision making regarding appropriate practice, although they can set bounds on alternatives; patient values and preferences should have a substantial influencing role.
No recommendation	No recommendation means there is a lack of pertinent evidence (grade D)* and an unclear balance between benefits and harms.	Clinicians should feel little constraint in their decision making and be alert to new published evidence that clarifies the balance of benefit vs harm; patient preferences and values should have a substantial influencing role.

Category of Evidence

Ia Evidence from meta-analysis of randomized controlled trials
Ib Evidence from at least 1 well-designed randomized controlled trial
Ic Evidence from at least 1 randomized controlled trial that was not very well designed
IIa Evidence from at least 1 controlled study without randomization
IIb Evidence from at least 1 other type of quasi-experimental study
IIc Evidence from one of the above that was not very well designed
IIIa Evidence from well-designed nonexperimental descriptive studies, such as comparative studies
IIIb Evidence from nonexperimental descriptive studies, such as comparative studies, that were not very well designed

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parameter is sent for review by invited reviewers and by anyone with an interest in the topic by posting the document on the Web sites of the ACAAI and the AAAAI.
The Joint Task Force has made a concerted effort to acknowledge all contributors to this parameter. If any contributors have been excluded inadvertently, the Task Force will ensure that appropriate recognition of such contributions is made subsequently.

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IVa Evidence from expert committee reports and/or opinions or clinical experience of respected authorities

*Strength of Evidence**

A Directly based on category I evidence that is well designed
B Directly based on category II evidence or recommendation from category I evidence that is not well designed
C Directly based on category III evidence or recommendation from category II evidence that is not well designed
D Directly based on category IV or recommendation from category III evidence that is not well designed
LB Laboratory based
NR Not rated

How This Practice Parameter was Developed

The Joint Task Force on Practice Parameters

The Joint Task Force on Practice Parameters (JTF) is a 13-member task force consisting of 6 representatives assigned by the American Academy of Allergy, Asthma & Immunology; 6 by the American College of Allergy, Asthma & Immunology; and 1 by the Joint Council of Allergy and Immunology. This JTF oversees the development of practice parameters; selects the workgroup chair(s); and reviews drafts of the parameters for accuracy, practicality, clarity, and broad utility of the recommendations for clinical practice.

The Anaphylaxis Parameter Workgroup

The Anaphylaxis Practice Parameter Workgroup was commissioned by the JTF to update the previous practice parameter. Dr Philip Lieberman invited workgroup members to participate in the parameter update who are considered experts in the field of anaphylaxis. Workgroup members have been vetted for financial conflicts of interest by the JTF and their conflicts of interest have been listed in this document and are posted on the JTF Web site (http://www.allergyparameters.org). Where a potential conflict of interest is present, the potentially conflicted workgroup member was excluded from discussing relevant issues.

Protocol for Finding Evidence

The charge to the workgroup was to use a systematic literature review, in conjunction with consensus expert opinion and workgroup-identified supplementary documents, to update the Practice Parameter on Anaphylaxis.

A search of the medical literature since 2010 (the date of the last edition of this parameter) was performed for different terms that were considered relevant to this practice parameter. In particular, search terms included *anaphylaxis, seminal fluid anaphylaxis, perioperative anaphylaxis, food allergy, mastocytosis, mast cell activation syndrome, idiopathic anaphylaxis, galactose 1-3 alpha galactose, epinephrine, hymenoptera allergy, latex allergy, anaphylactic shock, exercise anaphylaxis, drug allergy,* and *immunotherapy.*

An electronic search of databases, mainly PubMed, but also CENTRAL (Cochrane Central Register of Controlled Trials), Google Scholar, and Science Direct, was performed. In total 3,424 references were found. These were rated by giving preference for selection in the following order: meta-analysis, systematic reviews, randomized controlled trials, cohort studies, case–control studies, case series and case reports, and animal studies. Using these criteria, 382 new references were added.

Abbreviations

ACE inhibitors	angiotensin-converting enzyme inhibitors
AIE	Auto-injectable epinephrine
AIT	Allergen immunotherapy
alpha-gal	Galactose-α-1,3-galactose
EIA	Exercise-induced anaphylaxis
EMS	Emergency medical services
FAAN	Food Allergy and Anaphylaxis Network (now Food Allergy Research & Education)
FDEIA	Food-dependent exercise-induced anaphylaxis
MCAS	Mast cell activating syndrome
MMAS	Monoclonal mast cell activating syndrome
NIAID	National Institute of Allergy and Infectious Diseases
NSAID	Nonsteroidal anti-inflammatory drug
RCM	Radiocontrast material
SCIT	Subcutaneous immunotherapy
SM	Systemic mastocytosis
SR	Systemic reaction
UP	Urticaria pigmentosa
VIT	Venom immunotherapy
WHO	World Health Organization

Preface

This is the fourth iteration of this parameter entitled "The Diagnosis and Management of Anaphylaxis." The first anaphylaxis parameter was published in 1998 and the last in 2010. The objective of this parameter is to update these previous versions and ultimately to improve the care of patients by providing the practicing physician with an evidence-based approach to the diagnosis and management of anaphylactic events.

As always, the JTF and the contributing authors thank the ACAAI, AAAAI, and Joint Council of Allergy and Immunology, for their continued support of parameter development.

The JTF also thank the contributors to this parameter who have been so generous of their time and effort.

Since the last publication of the parameters, there have been several new developments that are discussed in this revision. To accommodate these developments, 4 new sections have been added to this edition:

1. A discussion on the definition of anaphylaxis
2. Controversies and unsettled issues related to anaphylaxis
3. Anaphylaxis in mastocytosis and monoclonal mast cell activating syndrome (MCAS)
4. Unusual presentations of anaphylaxis

With the addition of the new sections, this revision contains 11 chapters dealing with different forms of anaphylaxis in a format the editors believe is unique to all guidelines dealing with this disorder. These sections discuss the general evaluation and management of a patient with a history of anaphylaxis; office management of anaphylaxis; and anaphylaxis to foods, drugs, insect stings, seminal fluid, exercise, and allergen immunotherapy (AIT). In addition, there are sections on anaphylaxis related to mastocytosis, anaphylaxis occurring in the perioperative period, and unusual manifestations of this disorder.

The document is written so that a reader looking for information can simply choose to review only one of these sections, whereas a reader wanting a comprehensive review could start at the beginning of this document and become familiarized with almost all areas of this disorder that are of clinical importance. This format inherently results in some repetition and, inevitably, in some subtle differences of opinion between authors of each section (all of whom are well-recognized experts in their area of discussion). The editors believe repetition in this way is desirable because this allows the reader to be presented with all the recommendations in

the section they choose to read. For example, in several sections, there is a repetitive recommendation to supply patients who are at risk for anaphylaxis with an auto-injector for epinephrine. Thus, the Summary Statements will state this recommendation in several places. The editors believe this is desirable because many readers will choose to read only a single section when looking for information pertinent to a given patient.

Also, because of this repetition, another issue occurs, namely that of subtle disagreements. For example, some authors might judge that there are different strengths of recommendations or grades of evidence for a similar recommendation. The editors believe this adds rather than detracts from the strength of this document. They have judged that it is important for the reader to know that consensus opinion cannot be reached on all issues relative to anaphylaxis. There is simply not enough evidence in many instances to come to definitive conclusions. That is the reason for the addition of a section entitled "Controversies and Unsettled Issues Related to Patients at Risk for or Being Treated for Anaphylaxis."

Another example in which opinions can vary is in how long a patient should be observed after signs and symptoms of an episode of anaphylaxis have resolved. There is no definitive answer to this question and therefore experts might disagree. Such disagreements reflect differences in experiences and cannot be definitively adjudicated. Therefore, this disagreement has not been discouraged, but rather encouraged, in this document. The editors believe that expression of these subtle differences is healthy and should be left intact.

On occasion, the same or similar tables or statements might be present in 2 different sections. The editors believe it is important to the reader that each section remains complete for the reader who chooses to read only that particular section. It would be inordinately inconvenient for the reader to go back and forth through the document to find a given table.

Each section has its own set of references. Thus, as in a textbook, a reference can appear in several places in the text. Because it is important to have each section stand alone as a complete source of information, the editors believe it best for the reader to be able to access the references without having to search through the entire document.

Introduction and Considerations on the Definition of Anaphylaxis

To fully understand the current debate over the definition of the term *anaphylaxis* and the criteria necessary to establish its diagnosis, one must understand the history behind the development of the term.

The term was coined in 1901 by Charles Richet and Paul Portier to describe a phenomenon discovered while experimenting with aqueous glycerin extracts of the sea anemone.

It was their intent to "immunize" dogs to the venom of the sea anemone. In doing so, they found that the "opposite effect" was produced. That is, dogs developed an increased sensitivity to the venom with readministration after a course of "immunization" injections. Because they produced the opposite of their original intent, prophylaxis, they called the phenomenon *anaphylaxis* (*ana* being Greek for "against" or "opposite"; *phylaxis* being Greek for "protection").[1,2]

The term *anaphylaxis* gained rapid clinical recognition, and by 1925 Arthur Coca[3] devoted a chapter to this condition in his immunology text. With the increased use of medications, it became evident that anaphylactic reactions could readily occur in human beings, and in 1945 Robert Cooke[4] defined anaphylaxis as "a special or particular immunologic type of induced protein (or hapten) sensitivity in man or experimental animals and may properly be considered as a subdivision of Allergy."

With the discovery of immunoglobulin E (IgE), it became apparent that anaphylactic reactions were in many instances mediated by this antibody. However, not all episodes could be attributed to an IgE-mediated mechanism. Thus, it was realized that the clinical expression characteristic of an anaphylactic episode had more than 1 mechanism of production, and the term *anaphylactoid reaction* was introduced to describe events that were clinically similar to but not mediated by IgE.[1] At that time (the 1970s), the definition of anaphylaxis became "a systemic, immediate hypersensitivity reaction caused by IgE-mediated immunologic release of mediators from mast cells and basophils." The recognition that non–IgE-mediated mechanisms could produce a clinically similar event spawned the descriptor "anaphylactoid." Thus, "the term 'anaphylactoid reaction' referred (and still does refer) to a clinically similar event not mediated by immunoglobulin E."

There were objections to this terminology, and in 2003 the World Allergy Organization suggested that the term *anaphylactoid* be abandoned and all such events, regardless of the mechanism of production, be called *anaphylactic episodes*. They further suggested that these episodes be divided into immunologic and nonimmunologic events. Nonimmunologic anaphylactic events could be considered synonymous with the term *anaphylactoid*, and the immunologic events were further subcategorized as mediated and not mediated by IgE.[5,6] However, there are problems with this terminology, and to date, the term *anaphylactoid,* which had become embedded in the lexicon, remains in use.

Despite this intense and well-meaning debate over the definition of anaphylaxis, problems still haunted efforts to find a completely acceptable terminology. For example, idiopathic anaphylaxis, which is responsible for a significant number of cases,[7] is not easily accounted for when using either of these 2 currently accepted definitions. Therefore, Simons[8] proposed a separate category that is neither immunologic nor nonimmunologic, but rather "idiopathic."

With these difficulties in mind, the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) and Food Allergy Research and Education assembled experts from multiple specialties including allergists and immunologists, emergency department physicians, intensive care physicians, pediatricians, and internists to establish clinically relevant criteria defining this condition that would be acceptable not only to the allergy community but also to all physicians managing this disorder. The results of this symposium were published in preliminary form in 2005[9] and in a more refined version in 2006.[10] The "definition" derived by this panel has been used to discern when an injection of epinephrine is indicated for the management of a patient exhibiting signs and symptoms of an anaphylactic event. Controversy arose over the "definition" as discussed in a publication sponsored by the World Allergy Organization.[3]

Their critique of the NIAID/FAAN document was based on the implication that the criteria for anaphylaxis developed by Cox et al[11] might exclude patients with clinical manifestations expressed by a single system only (eg, hives alone) after exposure to a likely allergen. Thus, a patient receiving immunotherapy who developed hives alone, using this criterion, might be excluded from the administration of epinephrine. It should be noted that the "2-system" expression of symptoms developed by the NIAID/FAAN study group was derived by compromise: "For some participants, the primary concern was that a simple clinical definition could not include all subjects with anaphylaxis (ie, that it would have less than 100% sensitivity); whereas for others, the more sensitive definitions came with an unacceptably high number of false-positive results (ie, the risk of calling mild-allergic reactions 'anaphylaxis')."[12]

Realizing this, the criteria established by Sampson et al[9] added a caution as follows: "Other presentations may also indicate anaphylaxis (eg, early presentation, general flushing)." This

caveat appeared in the preliminary report published in 2005. In the second, refined document, published in 2006,[10] another caveat was added: "There will undoubtedly be patients who present with symptoms not yet fulfilling the criteria of anaphylaxis, yet in whom it would be appropriate to initiate therapy with epinephrine, such as a patient with a history of near fatal anaphylaxis to peanut who ingested peanut and within minutes is experiencing urticaria and generalized flushing."[10] Thus, it can be seen that this document did recognize the need for the administration of epinephrine in a patient who was exposed to a likely allergen who experienced only a single-system (eg, cutaneous) manifestation of symptoms. In addition, the criteria used by the NIAID/FAAN workshop to diagnose anaphylaxis have been shown to be useful in an emergency department setting to accurately establish a diagnosis of anaphylaxis.[12] They were found to have a sensitivity of 96.7% and a specificity of 82.4% and demonstrated a positive predictive value of 68.6% and a negative predictive value of 98.4%.

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Controversies and Unsettled Issues Related to Patients at Risk for or Being Treated for Anaphylaxis

The practice parameters developed by the JTF are evidence-based documents that recommend diagnostic and treatment approaches for a given disease state. However, in many instances, evidence on which to base such recommendations is lacking. Therefore, in some cases in which evidence is lacking, recommendations for management are based on expert opinion and might encourage an individual physician or other health care provider discretion within a framework of different options. These instances can generate controversy that lead to uncertainties in the approach to patient management. Specific issues in regard to the management of anaphylaxis that meet this description will be discussed in this section. This section is intended to offer evidence-based data on both sides of controversial issues where possible.

However, for issues where there is a lack of high-quality evidence, recommendations are made based on expert opinion. There are management issues pertaining to anaphylaxis for which definitive recommendations cannot be made. The intent herein is to clarify the source of controversies and present available options to assist the reader in making decisions. Where possible, data relevant to these issues are discussed with consideration of the pros and cons of different management strategies. In the absence of high-quality evidence, management decisions rely to a greater extent on physician or other health care provider experience and patient circumstances. Where appropriate, patients should be given the opportunity to express their values and preferences and participate in the medical decision-making process.

1. Should patients receiving subcutaneous immunotherapy (SCIT) be prescribed auto-injectable epinephrine (AIE)?

This issue arises because it has been shown that anaphylactic reactions to SCIT can occur after the suggested 30-minute wait period.[1]

Given this observation, it might stand to reason that all patients receiving SCIT should receive a prescription for epinephrine. However, there are other factors to be considered. These include the additional cost and the practicality of patients keeping the injector with them.

For these and other reasons, there is no definitive recommendation as to whether an auto-injector should be prescribed. In fact, according to the limited available data, there are great variations in practice as to what percentage of allergists and immunologists prescribe epinephrine in this setting. According to a survey,[2] 13.5% of allergists and immunologists do not prescribe an AIE for their patients on immunotherapy, 33.3% prescribe it to all of their patients on immunotherapy, and 52.7% risk stratify their patients by disease severity, history of reactions, and type of immunotherapy. With this degree of variance in practice, it is obvious that there is no consensus of opinion on this issue.

The decision as to whether to prescribe epinephrine in this instance thus remains at the discretion of the physician.

2. Should individuals with large local reactions to insect stings be given an AIE?

Five present to 10% of patients experiencing large local reactions are at risk for a systemic reaction (SR).[3–6] In the most recent Practice Parameter on Stinging Insect Hypersensitivity,[3] the decision to prescribe an AIE is left to the discretion of the physician caring for the patient. Providing injectable epinephrine to patients who have a history of large local reactions for use if a subsequent SR occurs is usually not necessary but might be considered if it provides reassurance to the patient. This decision and the physician's judgment might be influenced by factors such as the potential risk of being stung, personal health issues (eg, the presence of cardiovascular disease), and the individual patient's preference. The question is, of course, Is a 5% to 10% risk sufficient to justify the additional cost, and would it be practical to expect a patient who has never experienced an SR to keep an automatic epinephrine injector on their person?

There are no data to assist in answering this question and thus the choice is left to physician discretion with patient input after consideration of benefit and burden.

3. Should patients with oral allergy syndrome (fruit-pollen syndrome) be given an AIE?

The oral allergy syndrome is an IgE-mediated condition that occurs in close proximity to the throat. The exact incidence of

anaphylaxis in patients with oral allergy syndrome is unknown, but in a review of multiple studies, it was estimated that the incidence ranges from 2% to 10% of patients.[7] However, in a survey of allergists and immunologists, 20% of allergists reported that some of their patients did develop systemic symptoms. Thirty percent never prescribed an AIE and 3% always did. The remainder prescribed an AIE based on the nature of the patient's symptoms.[8] Some authorities cite features that might increase the risk for a systemic event and thus affect the decision to prescribe an AIE.[9] These include:

A. A past SR
B. Reaction of any severity to cooked plant food.
C. An established allergy to peanut, tree nuts, or mustard
D. Reactions to particular foods if practicing in an area where that food is associated with a severe reaction, such as peach or apple in Mediterranean countries
E. A pharyngeal anatomy that might predispose to severe obstruction even with a mild degree of pharyngeal (laryngeal) swelling, such as large tonsils or a large tongue
F. Patients who have reported dysphagia or significant throat discomfort during previous reactions

It is clear that these recommendations are derived from reasonable conclusions based on experience and clinical judgment. At this point, there is no consensus on this issue. Therefore, the choice is left to physician discretion, and patients should be given the opportunity to express their values and preferences and participate in the medical decision-making process.

4. Should patients on angiotensin-converting enzyme (ACE) inhibitors be excluded from immunotherapy to hymenoptera venom?

Although there is some suggestion to the contrary,[10] there is evidence in the published literature that ACE inhibitors might be a risk factor for an increase in incidence and severity of anaphylaxis to hymenoptera stings and venom immunotherapy (VIT).[11–14] There is a warning in the package insert of venom extracts that taking an ACE inhibitor can predispose to an SR during VIT. Because patients who are taking these drugs often cannot discontinue them without risk of cardiovascular or renal problems, this issue in a patient with hymenoptera sensitivity undergoing immunotherapy presents a common and important concern.

The issue can be approached only by analyzing the risk-to-benefit ratio for each patient, and the decision as to whether to discontinue these drugs is up to the discretion of the allergist in discussion with the other involved consultants (cardiologists, nephrologists).

5. Should a child who develops a contact urticarial reaction on the face from a food allergen be supplied an AIE?

A few years ago, the Food and Drug Administration's approved indication for the prescription of an automatic epinephrine injector was changed from a patient who had experienced an episode of anaphylaxis to an individual who is at increased risk for an episode of anaphylaxis. Thus, a child who has experienced contact urticaria to, for example, egg might qualify to receive an automatic epinephrine injector. However, the risk of anaphylaxis in this situation has not been quantified.

It has been documented that automatic epinephrine injectors are often under-prescribed in children with food allergy and anaphylaxis.[15–17] However, it also has been argued that because the risk of a fatal reaction to food, especially in preschool children, "is remote" and prescriptions for automatic epinephrine injectors have increased significantly, it is "important to provide a perspective on the risk of death from food-induced anaphylaxis and use 'risk factors' to assist in making the decision as to whether or not an AIE is indicated rather than prescribing them 'carte blanche.'"[18]

In keeping with this opinion, it might be reasonable to use risk factors to assist in the decision to prescribe an AIE. Some risk factors that might increase the risk for or severity of an anaphylactic event in a child demonstrating contact urticaria to food have been identified. These include the presence of allergy to peanuts or tree nuts, asthma, and IgE-mediated sensitivity to multiple allergens.[19,20] In addition, the risk of an SR, but not its severity, can further be assessed by quantitating the size of the skin test reaction and by the quantitative determination of serum-specific IgE.[21]

Despite these observations, there is great variation in how physicians manage food allergy in children.[22] Specifically, there does not appear to be a consensus regarding the use of an AIE in children with contact urticaria to foods, and thus the decision is left to the discretion of the physician.

6. Should a patient presenting with mild systemic symptoms involving at least 1 system (eg, urticaria with mild gastrointestinal cramping) be treated with antihistamines and/or corticosteroids and observed rather than given epinephrine?

Anaphylactic fatalities are rare,[23,24] and in the vast majority of instances, patients will do well. Nevertheless, fatalities do occur and reactions presenting with mild symptoms can rapidly progress to cardiovascular and respiratory arrest. In addition, it is improbable that patients experiencing anaphylactic events would be protected by antihistamine or corticosteroid because the onset of pharmacodynamic activity of these 2 classes of drugs is too slow to prevent cardiorespiratory arrest. For example, fexofenadine (180 mg) given by mouth failed to exhibit any inhibitory effect on histamine-induced wheal and flare at 30 minutes and did not exhibit a 50% suppression of wheal and flare until more than 100 minutes after administration. Diphenhydramine at 50 mg administered intramuscularly did not show a 50% decrease in skin test expression until 51.7 minutes, and diphenhydramine at 50 mg administered orally did not demonstrate such a decrease until 79.2 minutes after administration.[25] As noted, these times are insufficient to prevent cardiorespiratory arrest or death. In the largest study of anaphylactic deaths to date, it was found that the median time to respiratory or cardiac arrest was 30 minutes for foods, 15 minutes for venom, and 5 minutes for iatrogenic reactions.[26] In another study of fatalities, death occurred within 60 minutes in 13 of 25 cases.[27] Thus, based on their pharmacodynamics activity, antihistamines or corticosteroids would not prevent cardiorespiratory arrest or death in many instances. In addition, antihistamines would only antagonize the effect of histamine, whereas there is ample evidence that other mediators such as platelet activating factor and kinins are associated with severe and potentially fatal reactions.[28,29] Unfortunately, at the initiation of symptoms, often one cannot predict whether an episode will rapidly progress.[30] Because the clinical course of anaphylaxis can be unpredictable, prompt and early use of epinephrine should be considered even with mild symptoms or single-system involvement.

7. Should an elderly patient with hypertension and/or arteriosclerotic heart disease who is at risk of an episode of anaphylaxis be given an AIE? Also, should such a patient experiencing an episode be treated with epinephrine?

The pharmacologic effects of epinephrine are well known, and the fact that it increases vasoconstriction, vascular resistance, heart

rate, and force of contraction is beneficial in the treatment of anaphylactic episodes. However, these effects can be detrimental in a person with arteriosclerotic heart disease and/or hypertension. The administration of epinephrine to treat episodes of anaphylaxis has been associated with the occurrence of myocardial infarction and acute coronary syndrome on rare occasions.[31,32] However, this might be due to "guilt by association" rather than cause and effect because there are abundant mast cells in the human heart and the mediators of anaphylaxis can produce coronary artery vasospasm, and infarction can occur as part of the natural history of an anaphylactic episode.[33,34]

Thus, physicians and other health care providers faced with treating anaphylaxis in a patient with cardiovascular disease are presented with a dilemma. However, there is no absolute contraindication to the administration of epinephrine as clearly stated in the Food and Drug Administration package insert for AIE. This includes patients with acute coronary syndrome, and although the risk-to-benefit ratio needs to be assessed with care in such patients, it usually favors the administration of epinephrine. Moreover, cardiovascular disease does not "forbid" the use of epinephrine in the treatment of anaphylaxis. Nonetheless, there are no means by which data can be collected to support this statement because clearly the problem does not lend itself to experimental analysis.

8. Auto-injectors are available in 0.3-mL (0.3-mg) and 0.15-mL (0.15-mg) doses. The package insert states that the 0.3-mg epinephrine dose is "intended for patients who weigh 15 to 30 kg (33–66 pounds)." In a child weighing less than 15 kg, should an automatic injector be used or should the caregiver be instructed to maintain an ampule or a multidose vial and a tuberculin syringe to be used to treat events?

Although there are no clear-cut answers to this question, dosing mistakes are not uncommon when epinephrine is administered by syringe, and nonmedical personnel can have difficulties using this method.[35–37] Thus, an automatic epinephrine injector is clearly the preferred means of achieving an accurate dose.

Also, it is important to note that the optimal dose of epinephrine is unknown. There have been no published dose–response studies documenting that the suggested dose of 0.01 mg/kg is indeed the "correct dose," and the origin of this suggested dosage regimen could not be found. In fact, before the advent of currently available automatic epinephrine injectors, the recommended doses of epinephrine varied considerably. In the early epinephrine literature, asthma was treated in adults with 1-mg doses and in infants weighing 25 pounds with 1/16th of the adult dose.[38] Variations of this dose ranging from 0.2 to 0.5 mg were recommended for the treatment of anaphylaxis as late as 1978.[39] There have been commercially available preloaded epinephrine injectors filled with a dose of 0.5 mg for the administration to adults, and this dose was well accepted as optimal for the treatment of anaphylaxis until the advent of automatic injectors. Thus, the actual optimal dosing regimen is unknown.

With these observations in mind, it would seem prudent to consider prescribing an automatic epinephrine injector in children who are experiencing an anaphylactic event who weigh less than 33 pounds.

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Executive Summary

This executive summary has been developed from the summary statements at the beginning of each section of the document. These summary statements contain the most important points from their respective sections as judged by the authors of each. The reader is referred to the full section for discussion and references pertaining to the points summarized in the Executive Summary.

Any patient who has experienced an episode of anaphylaxis should be evaluated to determine the causative agent. When the cause is not readily identified, the patient should be referred to an allergist or immunologist to conduct this evaluation. Any patient who has experienced anaphylaxis when the cause is not completely avoidable or cannot be determined should be supplied with an AIE and should be instructed in the use of this device and told to keep their AIE with them at all times. The patient should be taught to recognize the signs and symptoms of anaphylaxis and when to administer the injection and be given an anaphylaxis action plan. Because anaphylactic episodes might require more than 1 dose of epinephrine, all patients should carry 2 AIEs.

The patient should be instructed to wear and carry identification denoting the patient's condition (eg, MedicAlert, 2193 West Chester Pike, Broomall, PA 19008).

Individual risk factors should be taken into consideration. These include age, activity, occupation, hobbies, residential conditions, and access to medical care. It is important to consider the patient's level of anxiety, and attempts should be made to have patients gain confidence in their ability to treat any future event.

Pharmacologic prophylaxis such as glucocorticosteroids and antihistamines can be used in select situations such as in the prevention of anaphylaxis to drugs or biologic agents (eg, radiocontrast material [RCM]) or to prevent recurrent episodes of idiopathic anaphylaxis. It should be recognized that, especially in adults, a very significant portion of patients have anaphylactic episodes for which no cause can be determined. Desensitization procedures to perform the temporary induction of tolerance also can be used in certain situations (eg, penicillin allergy).

Patients should be educated about the presence of hidden allergens (eg, tree nuts in pie crust) and should be informed about cross-reactivity between allergens in drugs (eg, various β-lactam antibiotics) and foods (eg, lentils and peanuts).

Any patient subject to episodes of anaphylaxis should be counseled regarding the use of certain medications that could worsen any future event or complicate therapy (eg, β-adrenergic blockers).

The appropriate treatment of an acute event that might occur in a medical office requires planning and preparation. Plan for an appropriate office response to anaphylaxis by (1) educating staff and patients; (2) preparing an anaphylaxis emergency cart; and (3) developing an office action plan for anaphylaxis management to maintain proficiency. Prepare all office staff (clerical, nursing, and primary providers) to recognize and monitor the patient for the early signs and symptoms of anaphylaxis in preparation for epinephrine administration.

At the onset of anaphylaxis, (1) administer epinephrine intramuscularly in the mid-outer thigh; (2) remove the inciting allergen, if possible (eg, stop an infusion); (3) quickly assess airway, breathing, circulation, and mentation, and summon appropriate assistance from staff members; and (4) start, if needed, cardiopulmonary resuscitation and summon emergency medical services (EMS).

Epinephrine should be administered and then immediately thereafter EMS should be notified for patients having severe anaphylaxis and/or patients not responding to epinephrine. Recognize that more than 1 injection might be necessary in some patients.

The patient should be placed in a supine position, unless respiratory compromise contraindicates it, to prevent or counteract potential circulatory collapse. Pregnant patients should be on their left side. For maintaining hemodynamic stability, intravenous access is essential. Oxygen should be administered to patients with any respiratory difficulty.

There should be a rapid and ongoing assessment of the patient's airway status. Airway patency should be maintained using the least invasive but effective method (eg, bag-valve-mask). Intravenous fluid replacement with normal saline is indicated for patients with circulatory collapse and for patients who do not respond to intramuscular epinephrine. Hypotension of any degree should prompt the administration of intravenous fluid.

For respiratory symptoms not responding to epinephrine, nebulized β_2-agonists such as albuterol should be administered. In patients who are receiving β-adrenergic blocking agents, glucagon should be administered if there is a failure to respond to epinephrine.

H_1 and H_2 antihistamines or corticosteroids can be given as adjunctive therapy after the administration of epinephrine but are not indicated as initial treatment for anaphylaxis in place of epinephrine. Consider these agents as optional therapy.

The treatment and duration of the event should be individualized based on the result of constant monitoring. Longer periods of observation are indicated for patients who have a history of risk factors for severe anaphylaxis such as asthma, previous biphasic reactions, or a previous protracted anaphylactic event. Patients with these risk factors who do not respond to treatment should be observed for at least 4 to 8 hours. On release from treatment, all patients should be prescribed an AIE, given an anaphylaxis action plan, and educated in the symptoms that might indicate another reaction.

Foods are the most common cause of anaphylaxis, followed by drugs. The most common foods to cause anaphylactic events are peanuts, tree nuts, fish, shellfish, milk, and egg, but any food can produce a reaction. Thus, food should be considered a possible cause of an anaphylactic reaction in any patient experiencing an event. In addition, anyone who has experienced an anaphylactic event should be considered for allergy testing to foods. If this event is delayed several hours after a meal, one also should consider testing for IgE antibodies against galactose-α-1,3-galactose (alpha-gal). This is particularly true if there is a history of tick bites or if the preceding meal consisted of mammalian meat. This oligosaccharide allergen is expressed on tissues of all nonhuman mammals. Patients who have IgE anti–alpha-gal should be advised to avoid all mammalian meats.

It is not possible to predict the severity of any future event based on the severity of past events. Mild events can be followed by life-threatening events. There is no current diagnostic test that will adequately predict the severity of the next episode of anaphylaxis.

Some patients are at high risk for fatal food-induced anaphylaxis. Risk factors include (1) adolescents, (2) patients with a history of a reaction, (3) patients allergic to peanuts or tree nuts, (4)

patients with a history of asthma, or (5) those presenting with the absence of cutaneous symptoms.

The diagnosis of food-induced anaphylaxis should be based on signs and symptoms in association with likely or known exposure to a food allergen. Events mimicking anaphylaxis also can occur after the ingestion of food. For example, the ingestion of "spoiled" scombroid fish, owing to the high content of histamine, can produce reactions mimicking an anaphylactic event. During such events, the serum tryptase will not be elevated, but 24-hour urinary histamine can be increased.

Avoidance of the causative food and foods that might cross-react with the culprit is the mainstay of long-term treatment of food-induced anaphylaxis. At this time, immunotherapeutic treatments (eg, desensitization) remain a research tool. Currently, there is inadequate evidence available to analyze the long-term therapeutic benefit compared with risk.

As with all other causes of anaphylaxis, patients who have experienced an episode of anaphylaxis to foods should be supplied with AIEs, instructed in their use, taught the signs and symptoms of anaphylaxis, and given an anaphylaxis action plan.

Medications rival food for the most common cause of anaphylaxis. The most common classes of drugs producing anaphylaxis are (1) antibiotics, especially β-lactam antibiotics, and (2) nonsteroidal anti-inflammatory drugs (NSAIDs). Skin tests can be helpful in evaluating some drugs. When penicillin is suspected, skin tests can be performed to the major allergen (benzylpenicilloyl polylysine) in addition to penicillin G as a surrogate for the minor determinant allergens. The negative predictive value of such testing is 95% to 99%. Patients who are allergic to penicillin have a very low risk of reacting to cephalosporins, but life-threatening events have occurred when patients allergic to penicillin have been treated with cephalosporins.

Vancomycin can produce manifestations similar to anaphylaxis. However, these reactions are not mediated by IgE and usually can be prevented by administering the drug through a slow intravenous infusion.

Anaphylactic reactions to omalizumab can be delayed in onset and progressive. Therefore, patients receiving this drug should be observed for 2 hours after the first 3 injections and 30 minutes after subsequent injections. Any patient receiving omalizumab should be prescribed an AIE, taught the signs and symptoms of anaphylaxis, and given an anaphylaxis action plan. The patient should carry the AIE to the office when receiving the injection and should keep it on his or her person for 24 hours after the injection.

Skin testing also can be helpful in patients who have developed anaphylaxis owing to biologic agents. In patients who have had anaphylaxis to a biologic agent, if no therapeutic alternative exists, then consider rapid desensitization to induce temporary tolerance, recognizing that repeat desensitizations might be necessary depending on the interval between infusions.

For patients who have experienced an anaphylactic reaction to RCM, if future administration is needed, then use a lower osmolality preparation and premedicate patients with prednisone and antihistamines at the appropriate times.

Insect sting reactions also are common causes of anaphylactic events. Patients experiencing anaphylactic reactions to an insect sting should undergo skin testing to venom if the insect was a "flying hymenoptera" and to whole-body extract if it was a fire ant, but patients experiencing only large local reactions and children with only mild cutaneous SRs need not be tested. These groups generally do not require venom testing or VIT because the incidence of anaphylaxis on repeat sting is low (5–10%).

Any patient experiencing an anaphylactic event to a hymenoptera sting should have a baseline serum tryptase performed because such patients are at risk of having systemic mastocytosis (SM).

Venom skin tests are preferred because they are the most sensitive. However, in vitro testing is an important complementary procedure. Patients who have had an anaphylactic reaction to a sting but do not demonstrate a positive skin test reaction should have in vitro tests performed.

The level of skin test or in vitro test reactivity does not reliably predict the severity of a future sting reaction, and the diagnosis cannot be made based only on skin testing or in vitro testing. The history is essential because of asymptomatic venom sensitization. Such asymptomatic sensitization occurs in up to 25% of adults.

Venom immunotherapy is recommended for patients with systemic sensitivity to flying hymenoptera because this treatment is highly effective (80–98%). The treatment of fire ant hypersensitivity is conducted with whole-body extracts. They appear to provide adequate allergen concentration for reasonable efficacy.

Anaphylaxis during the perioperative period is unique in its characteristics. It can be difficult to diagnose because of the affected patient's inability to communicate, the skin is covered, and there is a decreased occurrence of skin manifestations. In addition, determining the causative agent is difficult because numerous medications are often administered simultaneously.

The most frequent causes of these events are neuromuscular blocking agents and antibiotics. The β-lactam antibiotics are the most frequent class involved. However, other agents can be responsible. These include barbiturates, opioids, supravital dyes, latex, and transfusions. Skin testing and in vitro testing can be helpful in discerning the responsible agent. Validated skin tests and/or in vitro techniques are available for several drugs, including neuromuscular agents, latex, and β-lactam antibiotics.

Seminal fluid anaphylaxis is relatively rare but a significant problem for those affected. Seminal fluid anaphylaxis is diagnosed based on history. An event occurring during or immediately after coitus with classic anaphylactic manifestations suggests the diagnosis. Skin testing with fresh whole human seminal plasma or its fractions can be performed. The specimen should be obtained from the male partner. Other underlying causes, such as allergy to natural rubber latex condoms or drugs passively transferred through seminal plasma, also should be considered.

Patients with postcoital local reactions to human seminal plasma can be treated by intravaginal graded challenge to dilutions of whole seminal fluid or by systemic desensitization to relevant seminal plasma proteins. Patients experiencing systemic seminal fluid plasma hypersensitivity should always have an AIE available and barrier protection should always be used.

The patient with seminal plasma allergy should be informed that that infertility does not appear to be linked to seminal plasma hypersensitivity, and they might be able to conceive by artificial insemination with washed spermatozoa.

A cause of anaphylaxis that is often missed is exercise. Patients can experience anaphylaxis owing to exercise of any type, including running, cycling, and resistance exercise. This condition should be distinguished from cholinergic urticaria, which occurs whenever body temperature is elevated. The latter can occur with a hot shower, whereas patients with exercise-induced anaphylaxis (EIA) can tolerate exposure to heat quite well.

In some patients with EIA, cofactors are needed for the event to occur. These cofactors include the ingestion of foods, NSAIDs (especially aspirin), and, rarely, in individuals with atopy, high pollen levels.

Patients who have EIA should avoid exercise in the immediate postprandial period especially if the events have been associated with the ingestion of food. They could undergo skin testing to determine whether a specific food is responsible.

It is important to note that these events can be inconsistent in their occurrence. They will not necessarily occur with each exercise regimen. Therefore, exercise challenge testing does not consistently reproduce symptoms and is not necessarily a useful part of the evaluation. Patients with these events should stop exercising immediately at the onset of symptoms, because continued exertion

can worsen the episode. All patients with this disorder should carry 2 AIEs whenever they exercise and should exercise with a partner who can recognize symptoms and administer the epinephrine.

Prophylactic treatment is inconsistently effective and often fails to prevent events. Therefore, such treatment cannot be trusted to eliminate the need for exercising with a partner or carrying an AIE.

Subcutaneous AIT can produce anaphylactic events. Therefore, patients undergoing this treatment should be advised about the risk of immediate and late-onset reactions (beginning after 30 minutes). Allergy injection therapy should be administered in a supervised clinic setting staffed by personnel trained in recognition and treatment of anaphylaxis, and the patient should be observed for at least 30 minutes after the injection.

Most fatal anaphylactic reactions to allergy injections have been reported in patients with uncontrolled asthma. Thus, patients with asthma receiving immunotherapy should have the state of their asthma assessed before each injection.

In patients receiving VIT, ACE inhibitors have been associated with an increased frequency of reactions and should be discontinued (substituted) whenever possible. Beta-adrenergic blocking agents also have been reported to be associated with more severe events and can interfere with the activity of epinephrine. Therefore, their discontinuation (substitution) should be considered. Patients who cannot discontinue β-blockers should be advised of the risks involved and the risk-to-benefit ratio should be carefully analyzed.

During the past decade, it has been recognized that patients with SM or monoclonal MCAS (MMAS) are at increased risk for anaphylaxis. Thus, any patient with repeated episodes of anaphylaxis with unknown cause should have a baseline (asymptomatic) serum tryptase assay because an elevated baseline serum tryptase suggests these diagnoses.

In addition, in such patients, a bone marrow biopsy should be considered. The biopsy should be evaluated by immunohistochemical staining and tagged antibodies to mast cell tryptase and CD2 and CD25 should be used to detect their presence on CD117 (KIT)-positive cells.

One should always be aware that anaphylaxis can present with unusual clinical manifestations such as somnolence and chest pain in children, chest pain in adults, and syncope and seizure without any other sign or symptom.

I. Evaluation and Management of Patients with a History of Anaphylaxis

Summary Statement 1: Evaluate any patient who has experienced an episode of anaphylaxis for which the cause is not readily identified to determine the cause and refer to an allergist or immunologist to conduct this evaluation. [Recommendation; D Evidence]

Summary Statement 2: Supply any patient who has experienced an episode of anaphylaxis for which the allergen cannot be easily and completely avoided with an AIE and instructions as to when and how to administer this injector and emphasize that they should carry 2 AIEs with them at all times. [Strong Recommendation; C Evidence]

Summary Statement 3: Instruct the patient to wear and/or carry identification denoting his or her condition (eg, MedicAlert, 2193 West Chester Pike, Broomall, PA 19008) and give the patient an anaphylaxis action plan. [Strong Recommendation; D Evidence]

Summary Statement 4: Individualize avoidance measures taking into consideration factors such as the patient's age, activity, occupation, hobbies, residential conditions, access to medical care, and level of personal anxiety. [Recommendation; D Evidence]

Summary Statement 5: Use pharmacologic prophylaxis such as glucocorticosteroids and antihistamines in select situations (eg, to prevent recurrent anaphylactic reactions to RCM or to prevent idiopathic anaphylaxis). [Recommendation; C Evidence]

Summary Statement 6: When necessary, induce a temporary tolerance (desensitization) in patients who have experienced anaphylaxis from medications. [Recommendation; C Evidence]

Summary Statement 7: Educate patients about hidden allergens and cross-reactivity between various allergens and drugs. [Recommendation; C Evidence]

Summary Statement 8: Counsel patients at risk for future episodes regarding the use of medications that could worsen an event or complicate therapy (eg, β-adrenergic blockers). [Recommendation; C Evidence]

The care of patients presenting for evaluation and management after an episode of anaphylaxis requires knowledge of the symptoms, pathophysiology, differential diagnosis, and prevention of anaphylactic episodes.[1–90]

An algorithm for the evaluation and management of a patient with a history of anaphylaxis is presented in Figure I-1.

Performing the History

To interpret the history adequately, it is essential to know the manifestations of anaphylaxis. These manifestations can best be ascertained by a review of published series on the topic.[1–13] A summary of the signs and symptoms as reported in these series, totaling 1,865 patients, is presented in Table I-1. These series include patients of all ages with EIA, idiopathic anaphylaxis, and other causes. The most frequently seen manifestations of anaphylaxis are cutaneous, occurring in 62% to 90% of reported cases. This figure differs from that published in previous parameters[14] based on a recently conducted survey.[13] In this survey, a lesser incidence of cutaneous manifestations was recorded by patients. Only 62% of these patients recalled, based on a telephone survey, cutaneous symptoms. Nonetheless, the absence of cutaneous symptoms speaks against a diagnosis of anaphylaxis but does not rule it out. Severe episodes characterized by rapid cardiovascular collapse and shock can occur without cutaneous manifestations.[27–29] It might be helpful to better assess the signs and symptoms of the reaction by interviewing friends and/or family members who might have been present during the event. In addition, it is important to note that anaphylaxis can present with unusual manifestations (see Section IX, Unusual Presentation of Anaphylaxis), such as syncope without any further sign or symptom.[10] In addition, based on studies limited to children, the incidence of cutaneous manifestations in children might be lower.[31,53] The essentials of the history are listed in Table I-2.

The history and the medical record should include the time of occurrence of the attack, the setting in which it occurred, any treatment required during the episode, and the duration of the episode. A detailed history of all potential causes should be obtained. This includes a list of ingestants consumed and/or medications taken within 6 hours of the event, any sting or bite occurring before the event, and whether the event occurred during exercise. The location (work vs home) and whether the event was related to exposure to heat, cold, or occurred during sexual activity also should be determined. The patient's atopic state should be noted because food-induced, seminal fluid-related, and idiopathic anaphylaxis episodes are more common in patients with than in those without atopy. In women, the history should include any relationship between the attack and their menstrual cycle. A return of symptoms after a remission should be noted because this could indicate a biphasic reaction,[5,32] which might require a prolonged period of observation if subsequent events occur.

Differential Diagnosis

The differential diagnosis (Table I-3) must be considered whenever the history is taken, even in patients with a history of

anaphylaxis. A comprehensive differential diagnoses is presented in Table I-3. Vocal cord dysfunction and panic attacks should be considered in the differential diagnosis.

Special attention in the differential diagnosis should be given to vasodepressor (vasovagal) reactions. Characteristic features of this reaction include hypotension, pallor, weakness, nausea, vomiting, and diaphoresis. Such reactions often can be distinguished from anaphylaxis by a lack of characteristic cutaneous manifestations (urticaria, angioedema, flush, and pruritus) and the presence of bradycardia during the vasodepressor reaction instead of tachycardia usually seen with anaphylaxis. However, it should be noted that bradycardia can occur during anaphylaxis.[14,47] This is probably due to the Bezold-Jarisch reflex, a cardioinhibitory reflex that has its origin in sensory receptors in the inferoposterior wall of the left ventricle. Unmyelinated vagal C fibers transmit the reflex. Bradycardia occurs immediately with a vasodepressor event, but in anaphylaxis, tachycardia often precedes the onset of bradycardia.[14,47]

Flushing episodes can mimic anaphylactic events. Several drugs and ingestants including niacin, nicotine, catecholamines, ACE inhibitors, and alcohol can induce flushing.[14,34,47]

Other conditions that cause flushing must be considered, including rosacea, gastrointestinal and thyroid tumors, carcinoid syndrome, pheochromocytoma, hyperglycemia, postmenopausal flush, alcohol-induced flushing, and the "red man syndrome" owing to the administration of vancomycin. Laboratory studies (Table I-4) can be helpful in establishing the diagnosing the diagnosis.

There is a group of postprandial syndromes that can mimic anaphylaxis, such as monosodium glutamate-induced reactions and reactions to scombroid fish. The latter is increasing in frequency,[14,35] and because it is due to histamine produced by histidine-decarboxylating bacteria that cleave histamine from histidine in spoiled fish, the symptoms can be identical to those that occur in anaphylaxis. However, the cutaneous manifestation might be more of a flush (sunburn-like) than urticaria. Symptoms might affect more than 1 individual because anyone eating the fish can be affected. Serum tryptase levels are normal.

Not infrequently, nonorganic disease can mimic anaphylactic episodes. Such events can be involuntary (panic attacks), undifferentiated somatoform anaphylaxis,[14,56,76,77] and vocal cord dysfunction syndrome. On rare occasions, events can be self-induced as a variation of Munchausen syndrome. Undifferentiated somatoform anaphylaxis describes the presentation of manifestations mimicking anaphylaxis but without objective confirmatory findings. Like other somatoform disorders, this condition is related to psychological problems.

There are other conditions that can mimic anaphylaxis. For example, patients with hereditary angioedema often can have evanescent cutaneous findings that can be confused with urticaria. Other rare disorders such as capillary leak syndrome and paradoxical pheochromocytoma also must be considered under the differential diagnosis.

Using Tests and Procedures to Establish the Diagnosis of Anaphylaxis and its Cause

Laboratory tests useful in establishing the diagnosis and cause of an anaphylaxis are listed in Table I-4.

The most useful laboratory test to confirm a diagnosis of anaphylaxis at the time of an event is probably serum tryptase. However, at least in 1 study,[38] determination of plasma histamine was more sensitive than serum tryptase. In this study, elevations of plasma histamine were observed in 42 of 97 patients, whereas only 20 had elevations of tryptase. Patients with elevated histamine were more likely to have urticaria, more extensive erythema, abnormal abdominal findings, and wheezing. The advantage of measuring 24-hour urinary histamine metabolites rather than plasma histamine is the fact that by the time most patients are seen, plasma histamine levels have returned to normal because they remain elevated for only 30 to 60 minutes. This is the reason that tryptase is measured in most instances rather than plasma histamine. Tryptase levels peak 60 to 90 minutes after the onset of symptoms and remain elevated for at least 5 hours.

Total tryptase levels can be elevated in conditions other than mastocytosis and anaphylaxis, such as acute myelocytic leukemia, hypereosinophilic syndrome associated with the F1P1 L1-PDGFRA mutation, myelodysplastic syndromes, end-stage renal disease with endogenous stem cell factor elevation, and acquired C1 esterase deficiency in association with non-Hodgkin lymphoma.[36]

Prostaglandin determinations are commercially available and can be of value in diagnosing anaphylactic events.[57] In a study of patients with SM who experienced anaphylaxis, it was found that mast cell activation could be manifested by a selective excessive release of prostaglandin D_2. Of note is that these patients responded to the administration of aspirin but not to antihistamines.[57]

Further studies can be obtained should other diagnoses be suspected. For example, flushing without pruritus or urticaria suggests carcinoid syndrome or the presence of a vasointestinal polypeptide tumor or even perhaps a paradoxical reaction to a pheochromocytoma.

In this instance, the measurement of neuropeptides can be helpful. Chromogranin A is a precursor to several functional peptides including pancreastatin. It is elevated in carcinoid syndrome and can be elevated in pheochromocytoma.

Other neuropeptides can be elevated in gastrointestinal-secreting vasointestinal polypeptide tumors. Such tumors produce abdominal cramping pain, diarrhea, nausea, and intermittent episodes of flushing. Measurement of neuroendocrine hormones including vasointestinal polypeptide, neurokinin A, substance P, pancreastatin, and others is readily available. In addition, computed tomography, magnetic resonance imaging, and single-photon emission computed tomography can be helpful. These can be assisted by the administration of octreotide or pentetreotide, which binds to tumors, enhancing their detection.[59] To diagnose a pheochromocytoma, 24-hour urinary catechol, serum catechol, and plasma-free metanephrine (the test of choice) levels are measured.[60]

Tests to establish the cause of an event include skin and in vitro tests for serum specific IgE to foods and drugs, serum IgE to alpha-gal, baseline serum tryptase, 24-hour urinary histamine metabolites, prostaglandin D_2, oral challenges, and, in some cases, a bone marrow determination.

On occasion, fresh-food "prick-to-prick" testing is more sensitive than testing with commercial extracts and has been used to identify a food culprit undetected by testing with commercial extracts.

Recent advances that have altered the approach to the use of the laboratory to establish a causative agent are the discovery of the role of alpha-gal and the importance of mastocytosis and mast cell activating disorders as causes of anaphylactic events.

A novel IgE antibody to a mammalian oligosaccharide has been discovered that is associated with 2 distinct forms of anaphylaxis, an immediate onset of an event to cetuximab and a delayed onset of anaphylaxis, usually occurring 3 to 6 hours after the ingestion of mammalian food products (eg, beef and pork).[61] This oligosaccharide, alpha-gal, is a major blood group substance of nonprimate mammals and a well-known target of IgG antibodies that are present in the serum of all immune-competent individuals. Sensitization appears to occur through tick bites. The predominant cause of these IgE antibodies in the United States is bites from the Lone Star tick (*Amblyomma americanum*), but cases have been reported from other countries from other species. It is interesting that this IgE antibody to alpha-gal cross-reacts with cat and dog but does not appear to pose a risk for asthma. However, it can impair diagnostic testing in some situations. Of importance is that IgE anti–alpha-gal is usually not detected by skin tests using commercially available

extracts of mammalian meat, but there is a commercially available test to detect serum specific IgE anti–alpha-gal. A significant number of previously considered idiopathic anaphylactic events are due to this mechanism.[61]

Alpha-gal is a suspected culprit in any case without known cause, especially in events occurring a few hours after eating, particularly those beginning in the early morning hours.

The realization that mastocytosis and mast cell activating disorders can be responsible for episodes previously thought of as idiopathic has altered the approach to patients. The seminal article establishing a relation between mastocytosis and mast cell activating disorders was published in *Blood* in 2007.[62] In this article, patients with idiopathic anaphylaxis had a clonal disorder of mast cells. The investigators reported on 12 patients with idiopathic anaphylaxis who did not have characteristic bone marrow biopsy results characteristic of mastocytosis. That is, the biopsy results did not meet the criteria established by the World Health Organization (WHO) cited as necessary to establish a diagnosis of this disorder (Table I-5). However, some patients did demonstrate at least 1 minor criterion for mastocytosis. Some showed positivity for the 816D>V mast cell activating mutation. Since that publication, other studies confirming this observation have been published. These observations have prompted a proposed change in the nosology and classification of anaphylactic events.[63] The new proposed nosology was derived at an international conference convened to establish consensus-based, evidence-supported diagnostic criteria for MCASs.

This proposed nosology suggests that mast cell activating conditions be classified into 3 distinct categories:

1. Mastocytosis and mast cell activating disorders
2. IgE-mediated anaphylactic events
3. Idiopathic anaphylactic episodes

Mast cell activating disorders resemble mastocytosis and can cause anaphylaxis but lack sufficient bone marrow findings to make a diagnosis of mastocytosis according to the criteria established by the WHO[64] (Table I-5). Such patients exhibit some bone marrow findings seen in mastocytosis and can have gain in function mutations in c-kit. The diagnostic criteria for a diagnosis of a mast cell activating disorder[63] are listed in Table I-6.

The importance of establishing that mastocytosis and mast cell activating disorders can be the cause of idiopathic anaphylaxis is the fact that mast cell activating disorders can, on occasion, be controlled with tyrosine-kinase inhibitors and that, in the future, a tyrosine-kinase inhibitor that can control SM might be developed.

Baseline elevations in serum tryptase, plasma histamine, 24-hour urinary histamine metabolites, or prostaglandin D_2 suggest these conditions. The traditional cutoff value of 20 ng/mL used to establish an elevated level of serum tryptase might be too high. Mastocytosis and mast cell activating disorder can be present in patients with lower levels of serum tryptase. A study of patients who had hymenoptera anaphylaxis found that a level of 11.7 ng/mL was a marker for underlying mastocytosis.[65]

A screening test performed on blood to detect the 816V mutation can establish mastocytosis in most cases,[23,24] but the most definitive way to make a diagnosis of mastocytosis is to obtain a bone marrow biopsy specimen.

Thus, one is faced with the decision of whether to perform a bone marrow biopsy examination in patients in whom no cause for anaphylaxis has been determined. When to do so remains a cause of debate. However, there is growing importance regarding making such a diagnosis because some MCASs and some cases of mastocytosis that are negative for 816V can be treated with tyrosine-kinase inhibitors.[22,25,26]

To confirm a diagnosis of anaphylaxis in patients who have experienced an event, these patients should be given a letter stating that measurement of serum tryptase, plasma histamine, 24-hour urinary histamine metabolites, and perhaps prostaglandin D_2, depending on the capabilities of the emergency department, should be obtained.

It has been proposed that elevations of postmortem serum tryptase be used to establish anaphylaxis as a cause of death.[42] However, it should be clearly noted that postmortem elevation of serum tryptase concentrations is not a specific finding and therefore cannot be considered diagnostic of an anaphylactic death. There are reports of non-anaphylactic deaths with elevated postmortem serum tryptase levels.[43–45] Thus, the presence of an elevated postmortem tryptase level cannot be considered pathognomonic for a death owing to anaphylaxis. Moreover, the absence of an elevated serum tryptase postmortem cannot be considered sufficient to rule out anaphylaxis as the cause of death. In patients with a possible anaphylactic reaction to food, leftover or vomited food might be useful as a source of antigen for the creation of an in vitro test reagent.

Prevention and Management of Further Episodes

Some anaphylactic reactions are so severe that treatment is unsuccessful and death occurs. This underscores the critical importance of education, avoidance, and prevention (Table I-7). Therefore, patients should be educated regarding avoidance measures for known or suspected triggers of anaphylaxis. This should take into consideration factors such as the patient's age, concomitant conditions, activity, occupation, hobbies, residential conditions, access to medical care, and level of personal anxiety. Education should emphasize hidden allergens, cross-reactivity between various food or drug allergens, and unforeseen risks during medical procedures.

Patients discharged from emergency care of anaphylaxis should receive instruction on prevention of future episodes and when and how to administer AIE, with an understanding that these measures are not a substitute for emergency medical attention during anaphylaxis. Similar instruction of family, friends, and teachers or other caregivers (if applicable) could be optimal. After emergency treatment, the patient should be seen in consultation by an allergist or immunologist to review potential causes, prevention, and treatment of subsequent episodes.

Awareness of risk factors for anaphylaxis is important in preventing the occurrence of such reactions. Major risk factors for anaphylaxis include, but are not limited to, a history of such reactions, patient exposure to the possible trigger(s), and atopic background. An atopic background could be a risk factor for seminal fluid anaphylaxis, exercise-induced and latex-induced anaphylaxis (and possibly IgE-independent reactions to RCM), but not anaphylactic reactions to medications. This is particularly important for patient avoidance of possible triggers.

Avoidance measures can be successful in any given patient if future exposure to known culprit allergens for that patient can be prevented. However, avoidance measures must be individualized, taking into consideration the patient's age, activity, occupation, hobbies, residential conditions, access to medical care, and level of personal anxiety.

Parenteral administration of medication usually produces more severe reactions than oral administration. Therefore, drugs should be administered orally whenever possible. If parenteral administration is required, the patient should remain under medical observation for 20 to 30 minutes after the drug or other biologic agent is given. One might consider a waiting period of 1 to 2 hours if a patient receives an oral medication in the office that the patient has never taken. Instances of anaphylaxis resulting from drug mislabeling are rare but do occur. Therefore, proper labeling of drugs is essential, and whenever a drug is the suspected cause of an

episode, the contents of the container should be checked against the label.

Patients who will be exposed to known triggers of a prior reaction can in some cases be protected by (1) pharmacologic prophylaxis, (2) allergen (ie, venom) immunotherapy, or (3) short-term desensitization. Anti-IgE therapy alone or in combination with other therapeutic modalities might assist in the prevention of some forms of anaphylaxis, but further study is needed to define that role. Oral immunotherapy or sublingual immunotherapy with food allergens (eg, peanuts, milk, or eggs) have been explored in scientifically rigorous trials, but these methodologies are not yet ready for use outside controlled trials approved by research ethics review boards. At times, pharmacologic prophylaxis can be used to prevent recurrent anaphylaxis. For example, regimens have been used successfully to prevent reactions to RCM and idiopathic anaphylaxis.

Special note should be given to the prevention of reactions to RCM in a patient who has had an anaphylactoid event to its administration and must receive a contrast reagent again. There is a question of whether skin testing is an effective means to select an agent that might be least likely to produce a repeat event. Although some studies have suggested that skin tests might be helpful in this regard,[79] the results of these investigations have not been confirmed,[80] and at this time there does not appear to be enough evidence to suggest the use of skin testing for this purpose.

Many pretreatment protocols have been used to successfully prevent recurrent reactions to RCM. These include an H_1 antagonist alone, prednisone alone, prednisone plus an H_1 antagonist, prednisone plus an H_1 antagonist and ephedrine, the combination of an H_1 and an H_2 antagonist, prednisone plus an H_1 antagonist and an H_2 antagonist, and prednisone plus an H_1 antagonist and an H_2 antagonist and ephedrine.[81] Perhaps the best studied of these is the one suggested in the present parameter, which consists of the use a lower osmolar preparation and premedication with 50 mg of prednisone by mouth 13, 7, and 1 hours before the procedure and 50 mg of diphenhydramine intramuscularly 1 hour before the procedure.[81] This protocol was derived in studies involving only adult patients. There are no studies involving pediatric patients, but the American College of Radiology Manual on Contrast Media 2013 update has suggested the following protocol: 0.5 to 0.7 mg/kg of prednisone orally 13, 7, and 1 hours before contrast injection and 1.25 mg/kg of diphenhydramine orally (up to a maximum of 50 mg) 1 hour before contrast injection.

They note that appropriate intravenous doses can be substituted in patients who cannot orally ingest medications (http://aegysgroup.com/wp-content/uploads/2014/03/170675431-2013-Contrast-Media-ACR-v-9.pdf?utm_source=download&utm_medium=website&utm_campaign=2013-Contrast-Media-ACR).

Any patient who has experienced an episode of anaphylaxis is at increased risk for further events. Therefore, all patients who have had an episode should be managed as follows:

1. A prescription for an automatic epinephrine injector, 4 of which are currently available (Table I-8), should be given to the patient, and the patient should be personally instructed in the use of the injector. It should be noted that the technique used to administer an automatic epinephrine injector can vary according to the type of injector.
2. Patients should wear identification jewelry (eg, MedicAlert Foundation, 2323 Colorado Avenue, Turlock, CA 95382).
3. An anaphylaxis action plan should be given to the patient. Various plans are available at the Web sites of the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology.
4. If there is any question about the diagnosis, the patient should be given a letter to be taken to the emergency department if another episode does occur. The letter should request determination of a serum tryptase level and possibly 24-hour urinary histamine and prostaglandin D_2 levels.
5. If the etiology of the original anaphylactic event was a drug, then the patient should be educated regarding drugs that might cross-react with the original culprit (eg, penicillin and other β-lactam antibiotics).
6. Consideration should be given to the discontinuation of any drug that might worsen an episode or complicate its treatment. Drugs with the potential of doing so include β-adrenergic blockers, ACE inhibitors, α-adrenergic blockers, some tricyclic antidepressants (eg, amitriptyline), and possibly monoamine oxidase inhibitors, angiotensin receptor blockers, and renin inhibitors.[6,17–19] Other risk factors that can increase the frequency or severity of a reaction or complicate the treatment also should be considered and modified when possible. These factors include age, asthma, comorbidities, use of alcohol, and presence of mastocytosis (Table I-9).
7. In any patient who has experienced an anaphylactic event, one should consider a referral to an allergist or immunologist. It has been demonstrated that such a referral can improve outcomes by further refining the diagnosis and establishing the cause of the event.[78]

Table I-1
Signs and symptoms of anaphylaxis[a]

Signs and symptoms	Percentage[b]
Cutaneous	
Urticaria and angioedema	62–90
Flushing	45–55
Pruritus without rash	2–5
Respiratory	
Dyspnea, wheeze	45–50
Upper airway angioedema	50–60
Rhinitis	15–20
Hypotension, dizziness, syncope, diaphoresis	30–35
Abdominal	
Nausea, vomiting, diarrhea, abdominal pain	25–30
Miscellaneous	
Headache	5–8
Substernal pain	4–5
Seizure	1–2

[a]Data were derived from the following references: Lieberman P, Nicklas R, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol*. 2010;126:477–480; Wood R, Camargo CA, Lieberman P, et al. Anaphylaxis in America: results from a national physician survey. *Ann Allergy Asthma Immunol*. 2012;109 (suppl):A20; and Boyle J, Camargo CA, Lieberman P, et al. Anaphylaxis in America: results from a national telephone survey. *J Allergy Clin Immunol*. 2012;129 (suppl):AB132.
[b]Percentages are approximations.

Table I-2
Essential features of history in the evaluation of a patient who has experienced an episode of anaphylaxis

A	Detailed history of ingestants (foods/drugs) taken within 6 h before the event
B	Activity in which the patient was engaged at the time of the event
C	Location of the event (home, school, work, indoors/outdoors)
D	Exposure to heat or cold
E	Any related sting or bite
F	Time of day or night
G	Duration of event
H	Recurrence of symptoms after initial resolution
I	Exact nature of symptoms (eg, if cutaneous, determine whether flush, pruritus, urticaria, or angioedema)
J	In a woman, the relation between the event and her menstrual cycle
K	Was medical care given and what treatments were administered
L	How long before recovery occurred and was there a recurrence of symptoms after a symptom-free period

Table I-3
Differential diagnoses: entities, in addition to anaphylaxis, and causative agents to be considered when a patient presents to your office with symptoms suggestive of an anaphylactic episode including anaphylaxis

Anaphylaxis	
A	Anaphylaxis from foods, drugs, insect stings
B	Anaphylaxis from physical factors (exercise, cold, heat)
C	Idiopathic (cause undetermined) anaphylaxis
Vasodepressor reactions (vasovagal reactions)	
Flushing syndromes	
A	Carcinoid
B	Vasointestinal polypeptide tumors
C	Mastocytosis and mast cell activating syndrome
D	Medullary carcinoma of the thyroid
Restaurant syndromes	
A	Monosodium glutamate
B	Scombroidosis
Nonorganic disease	
A	Panic attacks
B	Munchausen stridor (factitious anaphylaxis)
C	Vocal cord dysfunction syndrome
D	Undifferentiated somatoform anaphylaxis
E	Prevarication anaphylaxis
Miscellaneous	
A	Hereditary angioedema accompanied by rash
B	Paradoxical pheochromocytoma
C	Red man syndrome (vancomycin)
D	Capillary leak syndrome

Table I-4
Tests useful in establishing a diagnosis of anaphylaxis, a condition mimicking anaphylaxis, or establishing the causal event

1		Establishing anaphylaxis as a cause
	a	During an event obtain
		i Serum tryptase
		ii Plasma histamine
		iii 24-h urinary histamine metabolites
		iv Urinary prostaglandin D_2
2		Using the laboratory to establish a diagnosis of a condition mimicking anaphylaxis
	a	Serum serotonin
	b	Urinary 5-hydroxyindoleacetic acid
	c	Chromogranin A
	d	Vasointestinal polypeptide
		i Substance P, vasointestinal polypeptide hormone, urokinase A, pancreastatin, ect
		ii Computed tomography, magnetic resonance imaging, single-photon emission computed tomography (octreotide or pentetreotide assisted)
	e	24-h urinary catecholamines
	f	Serum catechols
	g	Plasma free metanephrine
3		Tests to establish the etiology of anaphylactic events
	a	Skin tests to foods to drugs when indicated
		i Skin tests using standard commercially available extracts
		ii Skin tests using fresh food
	b	Serum-specific IgE to foods and drugs when indicated
	c	Oral challenge
	d	Galactose-1,3-α-galactose
	e	Baseline serum tryptase
	f	Baseline 24-h urinary histamine metabolites
	g	Prostaglandin D_2
	h	Blood determination for 816V mutation
	i	Bone marrow

Table I-5
World Health Organization criteria for systemic mastocytosis[a]

The definitive World Health Organization diagnosis of systemic mastocytosis requires the presence of 1 major criterion and 1 minor criterion or 3 minor criteria.	
Major criterion	
Presence of multifocal dense aggregates of >15 mast cells as detected with tryptase or other special stains in bone marrow or other extracutaneous organs	
Minor criteria	
1	Atypical morphology or spindle shapes in >25% of mast cells in bone marrow sections, bone marrow aspirate, or other extracutaneous tissues
2	Mutational analysis of KIT showing a codon 816 mutation (eg, Asp816Val) in bone marrow, blood, or extracutaneous organs
3	Bone marrow or other extracutaneous mast cells expressing surface markers CD2 and/or CD25
4	Baseline serum tryptase levels >20 ng/mL

[a]From Swerdlow SH, Campo E, Harris NL, et al. Mastocytosis (mast cell disease). In: *World Health Organization (WHO) Classification of Tumours*. Vol 2. Lyon, France: IARC Press; 2008:54–63.

Table I-6
Suggested criteria for the diagnosis of mast cell activating syndrome

1	Symptoms typical of those produced by mast cell degranulation
2	Substantial transient increase in mast cell mediators (serum tryptase increase of 20% plus 2 ng/mL within 4 h of an anaphylactic event)
3	Response to agents attenuating production of activities of these mediators or diminishing their effects on the target organ

Table I-7
Prevention of further episodes

1		The patient who has experienced an episode to a drug should be educated regarding possible cross-reacting agents
2		If a food was the cause, the patient should be educated about cross-reactivity of foods (eg, peanuts and lupin flour)
3		Drugs that place patients at risk for a more severe episode or complicate therapy should be discontinued if possible. Potential agents include:
	a	β-adrenergic blocking agents
	b	Angiotensin-converting enzyme inhibitors
	c	Angiotensin blockers
	d	Monoamine oxidase inhibitors
	e	Certain tricyclic antidepressants
4		If the patient must be re-exposed to a drug to which an event occurred, specialized procedures such as desensitization and pretreatment can be performed

Table I-8
Available automatic epinephrine injectors in the United States

Product name (alphabetical order)[a]	Web sites
Adrenaclick	www.adrenaclick.com
Auvi-Q	www.auviq.com
Epinephrine injection, USP auto-injector (authorized generic of Adrenaclick)	www.epinephrineautoinject.com
EpiPen	www.epipen.com

[a]All these devices are available in doses of 0.15 and 0.3 mg.

Table I-9
Factors that can increase the risk for an anaphylactic event, increase its severity, or complicate its treatment[a]

Factor	Comment
Mastocytosis	Events due to mastocytosis are characterized by more frequent and more severe cardiovascular manifestations
Age	The elderly are at risk because of comorbidities and increased use of medications Infants are at risk because manifestations might not be detected Teenagers are at risk because of "risky behavior"
Asthma	Presence of asthma clearly increases the risk of fatal events and can increase the frequency of events
Atopy	It is clear that atopy increases risk because patients with atopy are at risk for food allergy, but they also appear to be at risk for events in general. For example, they are at risk for events owing to the administration of radiocontrast material.
Drugs	Numerous drugs can increase the risk for a severe reaction and can complicate therapy by interfering with or even accentuating the action of epinephrine (see text)
Alcohol	Impairs judgement and can diminish recognition of symptoms
Comorbidities	Presence of cardiovascular disease has been shown to predispose to fatalities and it is probable that other chronic conditions such as renal and pulmonary problems would do likewise

[a]Data were derived from references 16 through 19 and 79 through 90.

Annotation 1: Is the history consistent with a previous episode of anaphylaxis?

All individuals who have had a known or suspected anaphylactic episode require a careful and complete review of their clinical history. This history can elicit manifestations such as urticaria, angioedema, flushing, pruritus, upper airway obstruction, gastrointestinal symptoms, syncope, hypotension, lower airway obstruction, and/or other less common manifestations.

Of primary importance is the nature of the symptoms characterizing the event. Essential questions to be asked are:

1. Were there cutaneous manifestations (specifically pruritus, flushing, urticaria, or angioedema)?
2. Was there any sign of airway obstruction involving the upper or lower airway?
3. Were there gastrointestinal symptoms (ie, nausea, vomiting, or diarrhea)?
4. Were syncope or presyncopal symptoms present?

The absence of cutaneous symptoms puts the diagnosis in question because most anaphylactic episodes include cutaneous symptoms (Table I-2), although their absence does not rule out anaphylaxis. The history should concentrate on agents encountered before the reaction. Whenever appropriate, the information should be obtained from not only the patient but also from family members or other witnesses of the event. The complete sequence of events must be reviewed, with special attention paid to cardiorespiratory symptoms. Medical records, including medication records, often can be useful in evaluating the history, physical findings, and treatment of the clinical event. In addition, the results of any previous laboratory studies (eg, serum tryptase) could be helpful in making the diagnosis of anaphylaxis or distinguishing it from other entities.

Annotation 1A: Consider consultation with allergist or immunologist

Evaluation, diagnosis, and long-term management can be complex. The allergist or immunologist has the training and expertise to obtain a detailed allergy history; coordinate laboratory and allergy testing; evaluate the benefits and risks of therapeutic options; and counsel the patient on avoidance measures. For these reasons, patients with a history of anaphylaxis should be considered for referral to an allergy or immunology specialist.

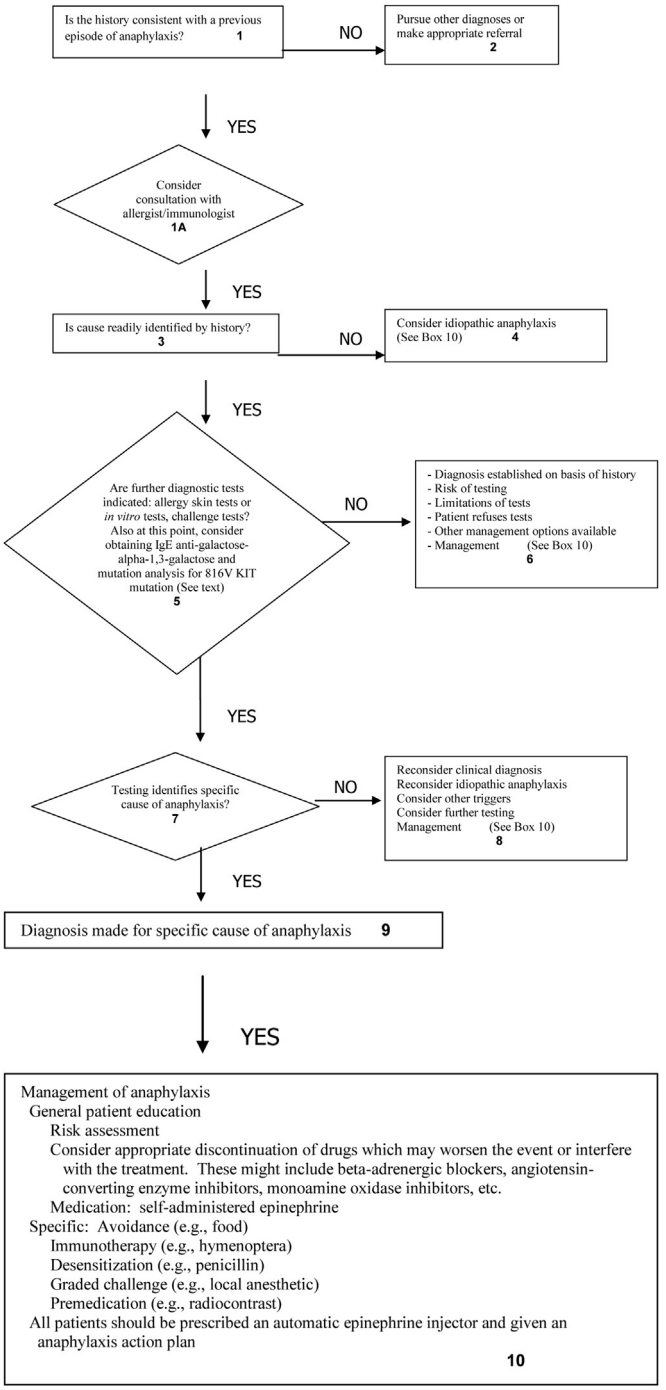

Figure I-1. Algorithm for initial evaluation and management of a patient with a previous episode of anaphylaxis.

Annotation 2: Pursue other diagnoses or make appropriate referral

Other conditions that should be considered in the differential diagnosis include (1) vasodepressor (vasovagal or neurocardiogenic) syncope, (2) syndromes that can be associated with flushing (eg, metastatic carcinoid), (3) postprandial syndromes (eg, scombroid poisoning), (4) SM, (5) psychiatric disorders that can mimic anaphylaxis such as panic attacks or vocal cord dysfunction syndrome, (6) angioedema (eg, hereditary angioedema), (7) other causes of shock (eg, cardiogenic), and (8) other cardiovascular or respiratory events.

Annotation 3: Is cause readily identified by history?

The history is the most important tool to establish the cause of anaphylaxis and takes precedence over diagnostic tests. A detailed

history of all food consumed and drugs taken during the 4 to 6 hours before the episode should be obtained. In addition, the labels for all packaged foods ingested by the patient in this period of time should be reviewed because a substance added to the food could be responsible. A history of any preceding bite or sting should be obtained. The patient's activities (eg, exercise, sexual activity) preceding the event should be reviewed. Patient diaries could be a useful adjunct in confirming or identifying the cause of anaphylaxis.

Annotation 4: Consider idiopathic anaphylaxis

Idiopathic anaphylaxis is a diagnosis of exclusion that should be made only after other causes of anaphylaxis and other differential diagnoses have been considered.

Annotation 5: Are further diagnostic tests indicated: allergy skin tests, in vitro tests, or challenge tests?

Skin tests and/or in vitro tests for specific IgE and challenge tests might be appropriate to help define the cause of the anaphylaxis. However, the history could be so conclusive that none of these tests are necessary.

Annotation 6: Diagnosis established based on history; risk of testing; limitation of tests; patient refuses test; other management options available; management

There might be circumstances in which skin tests or in vitro specific IgE and/or challenge tests might not be warranted. In general, this could apply when the clinician decides to proceed with management because the history is conclusive. The history of anaphylaxis to a specific agent might be so strong that testing is unnecessary and inappropriate from the risk-vs-benefit standpoint. If avoidance can be easily and safely accomplished, testing might not be necessary.

Testing or challenge with reagents to a suspected allergen might not be available or the predictive value of the test might be in question. Challenge tests (and, to a lesser extent, skin tests) can be hazardous and not acceptable from a risk-vs-benefit standpoint, if other management options are available. Occasionally patients might refuse to have the test.

Annotation 7: Testing identifies specific cause of anaphylaxis

Skin tests or in vitro tests can determine the presence of specific IgE antibodies to foods, medications (eg, penicillin and insulin), and stinging insects as a cause of anaphylaxis. For most medications, standardized in vivo and/or in vitro testing is not available.

In general, skin testing is more sensitive than in vitro testing and is the diagnostic procedure of choice for evaluation of most potential causes of anaphylaxis (eg, penicillin and insect stings). However, it is essential that the correct technique for skin testing be used. When possible, standardized extracts for skin testing should be used, although occasionally fresh-food extracts will be superior to available standardized extracts. If the skin testing extract has not been standardized (eg, latex, protamine, or antibiotics other than penicillin), the clinical relevance of the results might be uncertain. If skin testing is performed, then it should be done under the supervision of a physician who is experienced in the procedure in a setting with appropriate rescue equipment and medication.

The accuracy of in vitro testing depends on the reliability of the in vitro method, the ability to interpret the results, and the availability of reliable testing material. The clinical significance of skin testing or in vitro test depends on the ability to correlate the results of such testing with the patient's history.

If tests for specific IgE antibodies (ie, skin tests and/or in vitro tests) do not provide conclusive evidence of the cause of anaphylaxis, challenge with the suspected agent can be considered. Challenge procedures also might be appropriate in patients who develop non–IgE-mediated reactions (eg, reactions to aspirin or other NSAIDs). Challenge with suspected agents must be done carefully by individuals knowledgeable in the challenge procedure and with expertise in managing reactions to the challenge agent if they should occur.

Annotation 8: Reconsider clinical diagnosis; reconsider idiopathic anaphylaxis; consider other triggers; consider further testing; management

At this stage in the patient's evaluation, it is particularly important to consider other possible causes of anaphylaxis or a different diagnosis. The history and test results should be reviewed. Further testing for specific IgE antibodies should be considered. Laboratory studies that might be helpful include serum tryptase, urinary 5-hydroxyindoleacetic acid, urinary methylhistamine, chromogranin A, vasointestinal polypeptide, and catecholamines. Idiopathic anaphylaxis is a diagnosis of exclusion (see section on idiopathic anaphylaxis). Management of anaphylaxis should follow annotation 10 (see below).

Annotation 9: Diagnosis made of specific cause of anaphylaxis

The diagnosis of a specific cause of anaphylaxis can be supported by the results of skin tests, in vitro IgE tests, and/or challenge tests (particularly double-blinded, placebo-controlled challenge tests).

Annotation 10: Management of anaphylaxis

When anaphylaxis has occurred because of exposure to a specific agent (eg, food, medication, or insect sting), patients should be educated about agents or exposures that would place them at risk for future reactions and be counseled on avoidance measures that can be used to lower the risk for such exposures. Patients who have had anaphylactic reactions to food should be instructed on how to read food ingredient labels to identify foods that they should avoid. Patients with anaphylaxis to medications should be informed about all cross-reacting medications that should be avoided. Should there be a future essential indication for use of incriminated medications, it might be helpful to educate patients about applicable management options (eg, medication pretreatment and use of low osmolarity agents in patients with a history of reactions to RCM or desensitization for drugs such as antibiotics). Patients who have had an anaphylactic reaction to an insect sting should be advised about avoidance measures to decrease the risk of an insect sting and usually are candidates for insect VIT. Patients who have had anaphylaxis should carry self-injectable epinephrine if there is continued risk for anaphylaxis. Patients also should carry identification indicating that they have experienced anaphylaxis and indicating the responsible agent.

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II. Office Management of Anaphylaxis

Summary Statement 9: Plan for appropriate office response to anaphylaxis by (1) educating staff and patients, (2) preparing an anaphylaxis emergency cart, and (3) developing an office action plan for anaphylaxis management to maintain proficiency in anaphylaxis management. [Strong Recommendation; D Evidence]

Summary Statement 10: Prepare all office staff (clerical, nursing, and primary providers) to recognize and monitor the patient for the early signs and symptoms of anaphylaxis in preparation for epinephrine administration. [Strong Recommendation; D Evidence]

Summary Statement 11: At the onset of anaphylaxis, (1) administer epinephrine intramuscularly in the mid-outer thigh; (2) remove the inciting allergen, if possible (eg, stop an infusion); (3) quickly assess airway, breathing, circulation, and mentation and summon appropriate assistance from staff members; and (4) start, if needed, cardiopulmonary resuscitation and summon EMS. [Strong Recommendation; D Evidence]

Summary Statement 12: After administering epinephrine, notify EMS for patients having severe anaphylaxis and/or patients not responding to epinephrine. [Strong Recommendation; C Evidence]

Summary Statement 13: Place and maintain patients in a supine position, unless the respiratory compromise contraindicates it, to prevent or to counteract potential circulatory collapse. Place pregnant patients on their left side. For maintaining hemodynamic stability, intravenous access is essential. [Recommendation; C Evidence]

Summary Statement 14: Administer oxygen to select patients in anaphylaxis. [Strong Recommendation; C Evidence]

Summary Statement 15: Make a rapid and ongoing assessment of the patient's airway status and maintain airway patency using the least invasive but effective method (eg, bag-valve-mask). [Strong Recommendation; D Evidence]

Summary Statement 16: Initiate intravenous fluid replacement with normal saline for patients with circulatory collapse and for patients who do not respond to intramuscular epinephrine. [Strong Recommendation; C Evidence]

Summary Statement 17: In addition to epinephrine administered for anaphylaxis, consider administering a nebulized β_2-agonist (eg, albuterol) for signs and symptoms of bronchospasm. [Recommendation; B Evidence]

Summary Statement 18: In patients receiving β-adrenergic blocking agents, administer glucagon if they have not responded to epinephrine. [Strong Recommendation; C Evidence]

Summary Statement 19: Never administer H_1 and H_2 antihistamines or corticosteroids as initial therapy for anaphylaxis instead of epinephrine and consider these agents optional or adjunctive therapy. [Strong Recommendation; B Evidence]

Summary Statement 20: Individualize the duration of direct observation and monitoring after anaphylaxis but provide longer periods of observation for those patients with a history of risk factors for severe anaphylaxis (eg, asthma, previous biphasic reactions, or protracted anaphylaxis) for at least 4 to 8 hours. [Strong Recommendation; C Evidence]

Summary Statement 21: Prescribe AIE for patients who have experienced an anaphylactic reaction and for those at increased risk for anaphylaxis. [Strong Recommendation; C Evidence]

Summary Statement 22: Provide patients at risk for anaphylaxis with an action plan instructing them on how to manage an episode of anaphylaxis, including administration of epinephrine [Recommendation; C Evidence]

Education on the triggers and early signs and symptoms of anaphylaxis must be a structured, reoccurring, and scheduled process for all office staff, medical and clerical, and patients (Table II-1). The patient's education on anaphylaxis should start at the time of the new patient visit for all patients who present with signs and symptoms of anaphylaxis and for all patients who will be undergoing a diagnostic or treatment procedure that could result in anaphylaxis (eg, allergy skin testing). The educational process will involve obtaining consent, preferably written, for any invasive procedure (eg, SCIT) and will continue throughout the course of treatment. Staff and patients must recognize that any significant change in clinical status or the onset or increase of symptoms, however subtle, that occurs immediately after in-office AIT or diagnostic or therapeutic procedures, or possible ingestion of a known food or medication allergen should be considered anaphylaxis.[1] Anaphylaxis must be viewed as "a serious allergic reaction that is rapid in onset and may cause death" for which the only treatment is epinephrine.[2]

Appropriate management of anaphylaxis requires all offices that administer parental medications, including AIT, antibiotics, vaccines, and γ-globulin. These should be organized in such a way that they are readily accessible and can be easily moved to the patient experiencing anaphylaxis. Based largely on expert opinion, Table II-2 presents a list of the key anaphylaxis supplies and equipment that are considered (1) first line (required supplies and priority medications), (2) second line, and (3) third line (recommended for special settings). First-line items are a stethoscope, a sphygmomanometer, injectable epinephrine 1:1,000, oxygen, intravenous 0.9 normal (NL) saline, a 1-way valve facemask, oropharyngeal and nasal pharyngeal airways, disposable face masks, oxygen saturation monitor, albuterol inhalational solution (0.05%), glucagon, and the necessary supplies to administer these items. A written emergency protocol and flow chart for directing and recording times and events during treatment also should be considered first-line items.[3–7] Second-line supplies and medications include a mixture of what can be considered "optional" items (eg, antihistamines and corticosteroids) and advanced airway and cardiovascular support items (eg, laryngeal mask airways and an automated external defibrillator) that should be considered for maximum preparedness. Third-line supplies and medications are most

appropriate in areas in which EMS might be delayed by more than 10 minutes. The anaphylaxis cart must be inventoried on a regular basis (eg, every 3 months) and kept up to date by using the detailed listing of medications, supplies, and equipment as a checklist.

All allergists in their individual practice settings should collaborate with their nursing staff to develop a customized written protocol for the management of anaphylaxis in the office. Several action plans for anaphylaxis management in the office setting have been published.[4,6–8] A revised office-based anaphylaxis treatment protocol is presented in Table II-3. The anaphylaxis action plan should follow evidence-based guidelines and should provide a detailed stepwise approach based on symptoms and the patient's response to treatment. It can take the form of an algorithm, a table, a graph, or even a combination of these, but it must be easy to read and follow during an emergency. Ideally, it would include assigned roles for each staff member, by position or name, to be followed during anaphylaxis management. Once developed, it should be posted in all patient care areas of the office and with the emergency supplies for ready access.[8]

The importance of mock drills to deal with emergency situations is well recognized and used by hospitals (required annually by the Hospital Joint Commission under the jurisdiction of the Agency for Healthcare Research and Quality), public schools (eg, fire drills), airline pilots (eg, flight simulators), and emergency medical personnel (eg, disaster response drills), to name a few. Likewise, the successful management of anaphylaxis requires that office staff must immediately activate the response team and expeditiously deliver appropriate treatment.[6] This can be accomplished only with frequent (eg, periodic), organized, mock anaphylaxis drills in which all staff members, clerical and medical, are required to participate.[6,8]

Maintaining clinical proficiency with anaphylaxis management involves certification in basic cardiopulmonary resuscitation and, ideally, advanced life support to insure the proper skillset for treatment of refractory anaphylaxis, including airway management, cardiac compressions, venous and intraosseous access, and parental medication calculation and delivery.[6,9]

The initial assessment and treatment of the patient in anaphylaxis involves several critical steps that should be started concomitantly[4,6,10–12] (Table II-3). Urgent treatment is based on the finding that there is often a very short time (eg, 5 minutes for an iatrogenic intravenously administered allergen such as an antibiotic and 30 minutes for food-induced anaphylaxis) from the onset of mild symptoms to respiratory or cardiac arrest.[1]

Although removal of the inciting allergen is ideal, this will rarely apply in the office setting because parental or ingestion will usually have been completed before the onset of symptoms. However, with medication infusions or oral challenges with food or medications, the procedure should be stopped as soon as signs and symptoms of even mild anaphylaxis are noted.[4,13]

The first member of the office staff to recognize that the patient is experiencing anaphylaxis must be prepared to evaluate the airway, breathing, circulation, and mentation. If the patient has moderate to severe anaphylaxis or is showing signs and symptoms of impending cardiopulmonary arrest, EMS must be summoned immediately in addition to all available office medical staff. Cardiopulmonary resuscitation should be started immediately in the event of cardiopulmonary arrest, with emphasis on adequate chest compressions without interruption (Table II-4). Ventilations can be given once there are 2 medical staff members at the patient's side. For imminent or established cardiopulmonary arrest, rapidly establish venous access and administer an intravenous bolus dose of epinephrine because ventricular arrhythmias have been reported after epinephrine administration. For adults, the dose is 1 mg intravenously (as a 1:10,000 dilution). For a child, the dose is 0.01 mL/kg to a maximum single dose of 1 mg (give as a 1:10,000 dilution).[14,15] This can be repeated every 3 to 5 minutes as cardiopulmonary resuscitation is continued.[4,15,16] The same dose can be administered through the intraosseous route if an intravenous line cannot be established.[15] If the intravenous or intraosseous route is not available, epinephrine can be given by endotracheal administration if the advanced airway is in place. (Adult dose is 2–2.5 mg of 1:1,000 diluted in 5–10 mL of sterile water. Pediatric dose is 0.1 mg/kg to a maximum of 2.5 mg given as a 1:1,000 solution diluted in 5–10 mL of sterile water.[17])

The treatment of anaphylaxis is, at best, based on indirect and observational studies and primarily on consensus. Observational studies and analysis of near-fatal and fatal reactions have shown that prompt and decisive treatment of any SR, even a mild one, with epinephrine prevents progression to more severe symptoms.[6,18]

The most common trigger for anaphylaxis in the allergy office setting is the administration of SCIT. Having the patient under direct observation for 30 minutes offers the unique opportunity to observe for the early signs and symptoms of anaphylaxis. Rapid administration of a single dose of epinephrine for mild symptoms of anaphylaxis resulting from AIT almost always stops the progression of symptoms, with no additional epinephrine injections being required.[19]

In contrast, delayed administration of epinephrine is often believed to be the major contributing factor to fatalities.[1,20–26] In food-induced fatal to near-fatal anaphylaxis, it has been reported that of 7 of 13 children who survived, 6 had received epinephrine within the 30 minutes of ingesting the allergen. Of the 6 fatalities, only 2 children had received epinephrine within 60 minutes.[20]

Anaphylaxis guidelines are in agreement that epinephrine should be administered intramuscularly into the lateral thigh.[2,4,12,27–29] Published studies on epinephrine pharmacokinetics in patients not in anaphylaxis have shown that intramuscular administration in the vastus lateralis muscle produces a more rapid rate of increase in blood epinephrine levels than subcutaneous or intramuscular administration in the deltoid muscle. Unfortunately, there are no studies evaluating the pharmacokinetics of a subcutaneous injection in the lateral thigh. Moreover, it is not clear what the pharmacokinetics would be in patients in anaphylaxis and/or what the most desirable profile would be in that setting. Likewise, outcome measurements of therapeutic effectiveness of intramuscular vs subcutaneous injection are lacking and these might never be available owing to ethical concerns.

The adult dose of 1:1,000 epinephrine is 0.2 to 0.5 mL, whereas the pediatric dose is 0.01 mg/kg, with a maximum of 0.3 mg.[4,6,15,30,31] A higher dose (eg, 0.5 mL) within the recommended dose range should be considered in patients with severe anaphylaxis. If there has not been significant improvement in symptoms, then the dose can be repeated approximately every 5 to 15 minutes, as the physician deems to be necessary, usually moving to intravenous administration of epinephrine in conjunction with getting the patient to a medical setting where continuous monitoring can be done if there has been no response after 3 to 4 intramuscular injections. It has been shown that a repeat dose is required up to 35% of the time.[4,6,32,33]

Monitor and record the patient's blood pressure, cardiac rate and function, respiratory status, and oxygenation at frequent and regular intervals. Start frequent oxygen saturation measurement, start continuous noninvasive monitoring, and obtain an electrocardiogram, if available.[4]

There is universal agreement that most patients should be placed in a supine position during anaphylaxis.[4,6] However, whether to elevate the legs is controversial. Although some guidelines continue to recommend the Trendelenburg position (feet are elevated 15–30° higher than the head) for the management of shock, the American Heart Association and the American Red Cross in a 2010 consensus document concluded that there is insufficient evidence to support routine use of the Trendelenburg position in patients with

shock.[34] In the Prehospital Trauma Life Support Manual, the American National Association of Emergency Medical Technicians and the American College of Surgeons recommend using the supine position but explicitly discourage the Trendelenburg position or its variants for the management of shock.[35]

The proposed physiologic rationale for the Trendelenburg position is that it will shift intravascular volume from the lower extremities and abdomen to the upper part of the thorax, the heart, and the brain, thus improving perfusion to heart and brain. However, the evidence to support this rationale is very limited and often conflicting. In the normotensive patient and even the elderly patient who might have impairment of vasomotor control, placement in the Trendelenburg position does not demonstrate any deleterious hemodynamic effect and theoretically might help prevent hypotension.[36–39]

In contrast, patients with hypotension show no improvement in blood pressure, cardiac index, or tissue oxygenation with the use of the Trendelenburg position.[36,39–47] Potential complications of the Trendelenburg position for the normotensive and hypotensive patient include decreased lung compliance, vital capacity, and tidal volume; increase in arterial partial pressure of carbon dioxide; decreased arterial partial pressure of oxygen; and increase in the work of breathing.[39,44,46–49]

If the patient is having respiratory difficulty, consider having the patient sit up. There also is a possible increase in intracranial pressure associated with an increase in central venous pressure.[36,50–53] A recent systematic review of all articles on the effect of Trendelenburg position on hemodynamic status published before March 2011 concluded that the evidence was too inconsistent to support that the Trendelenburg position or even passive leg lifting as beneficial in hemodynamically compromised patients.[54] Given this conflicting evidence, it would seem prudent to place the patient in the supine position but without leg elevation.

In a retrospective study of 10 anaphylactic fatalities, there appeared to be an association with fatality when there was a change in position from a supine to an upright or standing position during anaphylaxis. Although the investigators recommended maintaining a supine position during anaphylaxis, they did not recommend the Trendelenburg position.[55]

Administration of oxygen is the second most important therapeutic intervention, second only to epinephrine administration, for the treatment of anaphylaxis and should be considered for all patients experiencing anaphylaxis regardless of their respiratory status.[6] It is imperative to administer oxygen for any patient with respiratory or cardiovascular compromise and to patients who do not respond to the initial treatment with epinephrine. Oxygen up to 100% should be administered at a flow rate of 6 to 10 L/min through a facemask. Ideally, oxygen saturation should be monitored and kept at 94% to 96% by oximetry.[4,13,56]

In most office settings, bag-valve-mask ventilation will be the method of choice to support ventilation in the event of respiratory failure or arrest. It is most effective when 2 individuals can support the airway. One person opens the airway with the head-tilt and chin-lift maneuver and seals the mask to the face, covering the nose and mouth. The second person squeezes the bag and the 2 rescuers look for adequate chest rise. It is recommended that approximately 600 mL of tidal volume for 1 second using an adult (1–2 L) bag be delivered. Supplementary oxygen at a flow rate of 10 to 12 L/min should be used. Two breaths are delivered during a 3- to 4-second pause after every 30 chest compressions.[57] An oropharyngeal airway can aid in the delivery of adequate ventilation in an unconscious patient with no cough or gag reflex. Improper insertion can result in displacement of the tongue into the hypopharynx, resulting in airway obstruction. The nasopharyngeal airway might be better tolerated by patients who are not deeply unconscious and can be of benefit when there is airway obstruction, but can cause airway bleeding in up to 30% of patients.[57,58] The training, skill, and experience of the physician should guide the selection of the most appropriate airway for the patient. When the provider can adequately ventilate the patient using the bag-valve-mask, there is no evidence that the use of advanced airway measures improves survival rates of out-of-hospital cardiac arrest.[57]

It is recommended that all Advanced Cardiovascular Life Support providers be trained and experienced in the insertion of 1 advanced airway because there will be times when the bag-mask is inadequate.[57] Advanced upper airway management can use the endotracheal tube or a supraglottic airway. The incidence of complications is unacceptably high when endotracheal intubation is performed by an inexperienced provider or monitoring of the tube is inadequate.[57] Use of a supraglottic airway (eg, laryngeal mask airway), esophageal-tracheal tube (Combitube), or laryngeal tube (King LT) is believed to be a reasonable alternative to the endotracheal intubation and its use can be accomplished without interruption of chest compressions.[57] In fact, for those trained in their use, these supraglottic airway devices are no more complicated to use than the bag-value-mask device because direct laryngoscopy of the airway is not required.[57] The supraglottic airway also offers some protection against aspiration. Some studies have shown that the laryngeal mask airway provides equivalent ventilation compared with the endotracheal tube.[59,60] There are no randomized clinical trials that have compared bag-valve-mask with endotracheal intubation in adult patients with cardiac arrest, but 1 such study in children showed no survival advantage for endotracheal intubation in the out-of-hospital arrest.[61]

In the hands of a very experienced provider, endotracheal intubation offers protection against aspiration and gastric insufflation, is the most effective method for ventilation and oxygenation, facilitates the use of suctioning, and allows for the delivery of drugs through the endotracheal tube. However, upper airway obstruction (eg, severe laryngeal edema) is an absolute contraindication for endotracheal intubation and should never be considered a substitute for a surgical airway in this setting. It has been suggested that inhaled epinephrine or intratracheally administered epinephrine might decrease oropharyngeal edema, making airway management less difficult.

The use of cricothyrotomy should be reserved for life-and-death situations when obstruction (eg, angioedema) above the larynx prevents adequate ventilation, even with the endotracheal tube. The use of the needle cricothyroidotomy, as a temporary airway, can be used for children and adults and is most likely the easiest for the inexperienced provider to use.[62] The procedures should take approximately 2 minutes to perform and makes use of a 14-gauge needle, syringe, canula, and Y-connector. If expiration is not possible through the cannula, then one should decrease the oxygen flow and limit use to shorter than 45 minutes because carbon dioxide retention will become significant.[63] A purpose-built kit (eg, Mini-Trach II) also could be considered but requires experience to use.[64]

Hypotension should be treated with rapid fluid replacement using 1 to 2 L of 0.9% normal saline, infused rapidly (eg, 5–10 mL/kg within the first 5 minutes for an adult and up to 30 mL/kg in the first hour for children).[6] Large-bore (14- to 16-gauge for adults) intravenous catheters should be used.[13] For the normotensive patient in anaphylaxis, starting NL saline at an appropriate maintenance rate for weight (eg, 125 mL/h for adults) to maintain venous access for medications and/or rapid fluid replacement is often unnecessary.[13]

Intravenous administration of epinephrine will rarely be necessary in the office setting and should be administered in a monitored setting with a programmable infusion pump to titrate appropriately.[65] However, if there is no response to multiple injections of intramuscular epinephrine and intravenous fluid

replacement in combination with a delay in EMS response, prolonged transport, or cardiopulmonary arrest and resuscitation, then intravenous epinephrine might be needed.[6] There is no established dosage or regimen for intravenous epinephrine in anaphylaxis.[6] However, a prospective study demonstrated the efficacy of a 1:100,000 solution of epinephrine intravenously by infusion pump at the initial rate of 2 to 10 μg/min titrated up or down depending on the clinical response or epinephrine side effects.[15,65] If an infusion of epinephrine is started in the office setting, then monitor by available means (eg, every-minute blood pressure and pulse and electrocardiographic monitoring, if available) and be prepared to treat ventricular arrhythmias.

Other vasopressors (eg, dopamine and vasopressin) have been suggested as alternative agents to epinephrine for treatment of refractory hypotension. However, there are no controlled studies that have evaluated the efficacy of these drugs in the treatment of anaphylaxis. Current recommendations are to start with an infusion of epinephrine for unresponsive anaphylaxis; and if there is refractory hypotension, then add dopamine as a second vasopressor, which would require a second infusion pump with continual electronic monitoring of heart rate and blood pressure. Although the administration of intravenous epinephrine will be introducing significant risk because most offices will not have an infusion pump or the ability to perform electronic monitoring, starting a second intravenous vasopressor drip should rarely, if ever, be considered in the office setting. Thus, expert opinion is to delay the use of dopamine or other vasopressors until the patient can be treated in a critical care setting, preferably in the hospital.

For signs and symptoms of bronchospasm (eg, wheezing, coughing, and shortness of breath) that has not responded to intramuscular epinephrine, administer albuterol (adult dose 2.5–5.0 mg/3 mL of saline; pediatric dose 2.5 mg/3 mL of saline) through a nebulizer and facemask. However, this treatment does not prevent or treat upper airway obstruction or laryngeal edema.[2,4,6,10,12]

Cases of unusually severe or refractory anaphylaxis (paradoxical bradycardia, profound hypotension, and severe bronchospasm) have been reported in patients receiving β-adrenergic blockers.[66–84] These systemic effects also have been documented with use of ophthalmic β-blockers.[85] Greater severity of anaphylaxis observed in patients receiving β-blockers might relate in part to a blunted response to epinephrine administered to treat anaphylaxis.[85] Epinephrine administered to a patient taking a β-blocker can produce unopposed α-adrenergic and reflex vagotonic effects, possibly leading to hypertension and the risk of cerebral hemorrhage.[86] In patients receiving β-blockers, increased propensity not only for bronchospasm but also for decreased cardiac contractility with perpetuation of hypotension and bradycardia is possible.[86–88] There are no epidemiologic studies that have indicated that anaphylaxis occurs more frequently in patients receiving β-blockers. Use of selective β_1-antagonists does not lower the risk of anaphylaxis because β_1- and β_2-antagonists can inhibit the β-adrenergic receptor.

If epinephrine is ineffective in treating anaphylaxis in patients taking β-blockers, then glucagon administration might be necessary.[81,89–97] Glucagon can reverse refractory bronchospasm and hypotension during anaphylaxis in patients on β-blockers by activating adenyl cyclase directly and bypassing the β-adrenergic receptor.[81,95–97] The recommended dosage for glucagon is 1 to 5 mg (20–30 mg/kg in children, maximum 1 mg) administered intravenously over 5 minutes and followed by an infusion at 5 to 15 mg/min titrated to clinical response. Protection of the airway is important because glucagon can cause emesis and risk aspiration in severely drowsy or obtunded patients. Placement in the lateral recumbent position provides sufficient airway protection for most of these patients.

Antihistamines, H_1 and H_2, should be considered second-line drugs in the management of anaphylaxis because there is no direct evidence to support their use in the treatment of anaphylaxis.[98,99] The use of the H_1 antihistamines is extrapolated mainly from their use in other allergic diseases (eg, urticaria or allergic rhinitis) in which they relieve itching, urticaria, flushing, sneezing, and rhinorrhea.[4] However, they do not prevent or treat upper airway obstruction or hypotension.[2,10,11,98,100–102] Although H_2 antihistamines have been studied in the treatment of anaphylaxis, their use is not supported by well-designed randomized, placebo-controlled trials.[4] When administered intravenously, some H_2 antihistamines (eg, cimetidine) can increase hypotension.[2,11,100] Furthermore, antihistamines, with a delayed onset of action, do not rapidly relieve the symptoms for which they do offer symptom relief (eg, urticaria).[9] The frequent and at times fatal error that is made by professionals and patients is to delay the administration of epinephrine while waiting for the antihistamines to relieve symptoms.[4,6,9,29] When administered as adjunctive treatment for severe anaphylaxis, only sedating antihistamines (eg, diphenhydramine) are available for intravenous administration. The dose for diphenhydramine is 25 to 50 mg in adults and 1 mg/kg to a maximum of 50 mg in children administered intravenously over 10 to 15 minutes.[4,6,9] When given orally, a low or nonsedating antihistamine (eg, cetirizine) is preferred over a sedating antihistamine (eg, diphenhydramine or chlorpheniramine) to avoid somnolence and impairment of cognitive function and the decreased ability to describe symptoms.[4,29] The onset of action of oral cetirizine is equal to or more rapid that that of oral diphenhydramine.[103] If administered parentally, then the dose of the H_2 antihistamine ranitidine is 1 mg/kg for adults and 12.5 to 50 mg in children and can be administered intramuscularly or intravenously (with slow infusion) because these administration methods have the same onset of action.[6]

The use of corticosteroids has no role in the acute management of anaphylaxis. The purported evidence that they produce a decrease of biphasic or prolonged reactions is not supported by strong evidence.[9,104–106] Their use and dosage are extrapolated from those used for acute asthma.[4] When administered, the intravenous or oral dosage often recommended is 1 to 2 mg/kg per dose up to 125 mg of methylprednisolone or an equivalent formulation. Patients who have complete resolution of symptoms after treatment with epinephrine do not need to be prescribed antihistamines or corticosteroids thereafter.[9]

The duration of direct observation and monitoring after an episode of anaphylaxis must be individualized and based on the severity and duration of the anaphylactic event, response to treatment, pattern of previous anaphylactic reactions (eg, history of protracted or biphasic reactions), medical comorbidities, patient reliability, and access to medical care.[9] Patients with moderate to severe anaphylaxis should be observed for a minimum of 4 to 8 hours.[4,9,29] Mild anaphylactic symptoms that occur in a medical setting (eg, office-based allergy injection) and that rapidly resolve with treatment usually will require a relatively shorter period of observation. A longer observation, including possible hospital admission, should be considered when (1) risk factors for more severe anaphylaxis (eg, history of severe asthma) are present, (2) the allergens have been ingested, (3) more than 1 dose of epinephrine is required, (4) pharyngeal edema is present, and (5) severe or prolonged symptoms (eg, prolonged wheezing or hypotension) are noted.[4,9,29]

At the time of discharge from medical supervision, patients should be provided with a prescription for AIE and instructed in its use. The patient must be instructed in the administration of epinephrine. Patients should be encouraged to fill this prescription immediately because up to 23% can experience a return of symptoms as a biphasic reaction, usually within 10 hours after the resolution of

Table II-1
Signs and symptoms of anaphylaxis

System	Symptoms	System	Symptoms
Skin	Flushing, local or generalized	Cardiovascular	Chest pain, eg, substernal, tachycardia, bradycardia, palpitations, arrhythmias, hypotension, feeling faint, urinary or fecal incontinence, shock, cardiac arrest
	Localized itching of skin or mucosa (local areas, eg, palms, genitalia, and/or palate) or generalized itching		
	Urticaria		
	Angioedema of skin or mucosa (eg, lips or tongue)		
	morbilliform rash		
	pilar erection		
	Conjunctival itching, redness, tearing, and/or swelling		
Respiratory	Nasal itching, congestion, rhinorrhea, sneezing	Central nervous system	Aura of impending doom
			Uneasiness
	Throat itching and tightness		Sudden behavioral change (eg, irritability)
	Dysphonia, hoarseness, stridor		Dizziness
	Coughing		Headache (eg, throbbing)
	Increased respiratory rate		Altered mental state
	Shortness of breath		Tunnel vision
	Wheezing		Confusion
	Chest tightness		Seizure
	Cyanosis	Other	Metallic taste in mouth
	Respiratory arrest		Uterine cramping and/or bleeding
Gastrointestinal	Abdominal pain (eg, cramping)		
	Nausea		
	Vomiting		
	Diarrhea		
	Dysphagia		

the presenting symptoms of anaphylaxis.[6,105] Two auto-injectors should be provided because up to 30% of patients who develop anaphylaxis will require more than 1 dose of epinephrine.[107,108] In the United States, auto-injectors are available in only 2 doses, 0.15 and 0.30 mg. The preferred adult dose is 0.30 mg. In children, the selection of the dose should be guided by the dose recommended for the first-aid treatment of anaphylaxis (0.01 mg/kg for children at a maximum of 0.30 mg) and individual risk factors and previous

Table II-2
Anaphylaxis emergency cart

Basic supplies	Airway & intravenous fluid support equipment	Medications
First line: required supplies and priority medications		
Written emergency protocol	Bag-valve-mask, self-inflating with reservoir (eg, Ambu bag) for adult and child[a]	Epinephrine 1:1,000 3 ampules or 1 multidose vial
Flow chart for recording times and events	Disposable face masks (infant, toddler, child, adult)	O_2 E-cylinder 2 and wrench; >1,100 psi
Stethoscope	Oropharyngeal airways: 6, 7, 8, 9, 10 cm	0.9% normal saline (2 1-L bags)
Sphygmomanometer, blood pressure cuffs (infant, child, adult, obese adult)	Nasal pharyngeal airway: 6,7,8, 9 mm	Albuterol inhalational solution 0.5%
Watch or clock	O_2 extension tubing	Glucagon 1 mg/mL (2 vials)
Gloves, preferably without latex[a]	O_2 nasal cannula	
Synthetic tape	Macro-drip administration set (10–15 drops/mL) and connection tubing	
Alcohol swabs	Intravenous pole or suitable substitute	
Tourniquets	Pulse oximeter	
Indwelling intravenous catheters (gauge 14, 16, 18, 20, 22)	Twin-jet nebulizer, face mask, tubing	
Intravenous butterfly needles (gauge 19, 21, 23)		
Syringes (1, 10, 20 mL)		
Needles 1–2 inches, 18, 21, 23 gauge		
Macro-drip administration sets		
Extension tubing		
T-connectors		
3-way stopcocks		
Arm boards (2–4 sizes)		
Second line: supplies and medications		
Automated external defibrillator	Laryngeal mask airways (sizes 2, 3, 4, 5)	Diphenhydramine 50 mg/mL intravenously
	suction machine and tubing	Cetirizine 10-mg tablets, 5 mg/tsp liquid
	cardiac arrest backboard	Ranitidine 25 mg/mL intravenously
		Methylprednisolone 125-mg vial
		Prednisone 5- or 10-mg tablets, prednisolone syrup 15 mg/tsp
Third line: supplies and medications		
Electrocardiograph and supplies	Equipment for intubation (for remote areas only)	Dopamine 200 mg/5 mL intravenously (1 ampule)
	5% dextrose in water 500 mL (for dopamine infusion)	Atropine 0.5 mg/mL intravenously

[a]Without latex when possible.

Table II-3
Anaphylaxis treatment protocol

Treatment of anaphylaxis in the physician's office		
Immediate measures		
1	Allergen	Remove the inciting allergen, if possible
2	Airway	Assess airway, breathing, circulation, and orientation; if needed, support the airway using the least invasive but effective method (eg, bag-valve-mask)
3	Cardiopulmonary resuscitation	Start chest compressions (100/min) if cardiovascular arrest occurs at any time
4	Epinephrine intramuscular	Inject epinephrine 0.3–0.5 mg (0.01 mg/kg for children) intramuscularly in the vastus lateralis (lateral thigh)
5	Get help	Summon appropriate assistance in office
6	Position	Place adults and adolescents in recumbent position; place young children in position of comfort; place pregnant patient on left side
7	Oxygen	Give 8–10 L/min through facemask or up to 100% oxygen as needed; monitor by pulse oximetry if available
7	Epinephrine intramuscular	Repeat intramuscular epinephrine every 5–15 min for up to 3 injections if the patient is not responding
6	EMS	Activate EMS (call 911 or local rescue squad) if no immediate response to first dose of intramuscular epinephrine or if anaphylaxis is moderate to severe (grade ≥2 on World Allergy Organization grading scale[4]
7	Intravenous fluids	Establish intravenous line for venous access and fluid replacement; keep open with 0.9 NL saline, push fluids for hypotension or failure to respond to epinephrine using 5–10 mg/kg as quickly as possible and up to 30 mL/kg in first hour for children and 1–2 L for adults
Additional measures		
8	Albuterol	Consider administration of 2.5–5 mg of nebulized albuterol in 3 mL of saline for lower airway obstruction; repeat as necessary every 15 min
9	glucagon	Patients on β-blockers who are not responding to epinephrine should be given 1–5 mg of glucagon intravenously slowly over 5 min because rapid administration of glucagon can induce vomiting
10	Epinephrine infusion	For patients with inadequate response to intramuscular epinephrine and intravenous saline, give epinephrine by continuous infusion by micro-drip in office setting (infusion pump in hospital setting); add 1 mg (1 mL of 1:1,000) of epinephrine to 1,000 mL of 0.9 NL saline; start infusion at 2 μg/min (2 mL/min = 120 mL/h) and increase up to 10 μg/min (10 mL/min = 600 mL/h); titrate dose continuously according to blood pressure, cardiac rate and function, and oxygenation
11	Intraosseous access	If intravenous access is not readily available in patients experiencing refractory anaphylaxis, obtain intraosseous access for administration of intravenous fluids and epinephrine infusion
Refractory anaphylaxis		
12	Advanced airway management	Use supraglottic airway, endotracheal intubation, or cricothyroidotomy for marked stridor, severe laryngeal edema, or when ventilation using the bag-valve-mask is inadequate and EMS has not arrived
13	Vasopressors	Consider administration of dopamine (in addition to epinephrine infusion) if patient is unresponsive to above treatment; this will likely be in the hospital setting where cardiac monitoring is available
Optional treatment (efficacy has not been established)		
14	H_1 antihistamine	Consider giving 25–50 mg of diphenhydramine intravenously for adults and 1 mg/kg (maximum 50 mg) for children; use 10 mg of cetirizine if an oral antihistamine is administered; once there is full recovery, there is no evidence that this medication needs to be continued
15	Corticosteroids	Administer 1–2 mg/kg up to 125 mg per dose, intravenously or orally, of methylprednisolone or an equivalent formulation; once there is full recovery, there is no evidence that this medication needs to be continued
Observation and monitoring		
16	Observation in hospital	Transport to emergency department by EMS for further treatment and observation for ––8 h
17	Observation in office	Observe in office until full recovery + additional 30–60 min for all patients who are not candidates for EMS transport to emergency department
Discharge management		
18	Education	Educate patient and family on how to recognize and how to treat anaphylaxis
19	Auto-injectable epinephrine	Prescribe 2 doses of auto-injectable epinephrine for patients who have experienced an anaphylactic reaction and for those at risk for severe anaphylaxis; train patient, patient provider, and family on how to use the auto-injector
20	Anaphylaxis action plan	Provide patients with an action plan instructing them on how and when to administer epinephrine

Abbreviations: EMS, emergency medical services; NL, normal.

anaphylactic events.[109,110] Given the safety profile of epinephrine use in children and the fact that underdosing might not effectively treat anaphylaxis, giving a dose that is slightly above the ideal dose appears to be a better option than giving a dose that is below the recommended dose.[109,110]

Although the initial anaphylaxis action plan can be provided at the point of care (eg, emergency department or primary care office), the permanent anaphylaxis action plan should be developed by the allergist working with the patient, the primary care physician, other members of the interdisciplinary clinical team (eg, nurse case manager), and the school, when appropriate. Although there are numerous examples of good action plans, using a standardized, peer-reviewed action plan such as those developed by the lay support groups in conjunction with the national allergy organizations is encouraged (http://www.foodallergy.org/document.doc?id=234; http://www.aanma.org/wordpress/wp-content/uploads/anaphylaxisactionplan.pdf).[111,112]

The action plan should indicate in simple, clearly stated language and/or figures the signs and symptoms of anaphylaxis, the patient's known triggers, and that the first and only mandatory drug to be administered is epinephrine, regardless of how mild the symptoms are. Further instructions to be listed in order are (1) call 911 and, if appropriate, (2) notify the patient's family. Whether to list on the action plan the administration of any medication other than epinephrine (eg, nonsedating antihistamines) should be left to the allergist who can decide, on a case-by-case basis, whether to include these medications, recognizing that one of the most common reasons given for the delay in epinephrine administration is that the patient or caretaker is "waiting to see if the antihistamine will work."

Table II-4
Cardio-airway-breathing

	Basic cardiopulmonary resuscitation is C-A-B—compressions–airway–breathing	
Check for pulse	Take for maximum of 10 s	
Chest compressions	push hard and push fast on the center of the chest	
	Maintain rate of 100/min	
	Compress chest 5 cm with each downstroke	
	Allow complete chest recoil between compressions	
	Minimize frequency and duration of any interruptions	
Ventilations	perform only if ≥2 rescuers are present	
	Avoid excessive ventilation—just enough to confirm chest rise	
	Deliver ventilation over 1 s	
	If 3 rescuers available—1 for compressions, 2 for bag-valve-mask and rotate positions every 2 min	
Compression/ventilation ratio	30/2	
Defibrillation	Single defibrillation using highest available energy in adults	Adult—200 J
Phases of resuscitation in cardiac arrest	Electrical phase 0–4 min	Defibrillate, compressions
	Hemodynamic phase 4–10 min after arrest	Defibrillate, compressions
	Metabolic phase >10 min after arrest	Few patients survive

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III. Anaphylaxis to Foods

Summary Statement 23: Consider food allergies in the etiology of anaphylaxis because they are a common trigger for anaphylaxis. [Recommendation; C Evidence]

Summary Statement 24: Recognize that peanuts, tree nuts, fish, shellfish, milk, and egg are the most commonly implicated foods, but that any food can theoretically trigger anaphylaxis. [Recommendation; C Evidence]

Summary Statement 25: Test patients with unexplained anaphylaxis or a known delayed SR to red meat for IgE specific antibodies for the oligosaccharide alpha-gal particularly if they have a history of tick bites, because this oligosaccharide allergen is expressed on the tissues of all nonhuman mammals. Advise patients allergic to alpha-gal to avoid all mammalian meats. [Recommendation; C Evidence]

Summary Statement 26: Do not instruct patients about the prognosis of food allergy and anaphylaxis based on the severity of a previous reaction to a food allergen or current diagnostic test reaction. [Recommendation; C Evidence]

Summary Statement 27: Recognize that some patients are at high risk for fatal, food-induced anaphylaxis, such as (1) adolescents, (2) patients with a history of reaction, (3) patients allergic to peanut or tree nuts, (4) patients with a history of asthma, (5) those presenting with the absence of cutaneous symptoms, or (6) those with delayed administration of epinephrine. [Recommendation; C Evidence]

Summary Statement 28: Make a diagnosis of food-induced anaphylaxis based on signs and symptoms in association with likely or known exposure to an allergen. [Recommendation; C Evidence]

Summary Statement 29: Recognize that anaphylactoid reactions such as ingestion of histamine from contaminated scombroid fish can produce reactions mimicking anaphylaxis. [Recommendation; C Evidence]

Summary Statement 30: Do not rely on elevated serum tryptase to make the diagnosis of food-induced anaphylaxis. [Recommendation; C Evidence]

Summary Statement 31: Insure that patients remain under medical supervision for a minimum of 4 to 8 hours to observe for recurrence of symptoms from anaphylaxis. [Recommendation; D Evidence]

Summary Statement 32: Prescribe 2 epinephrine auto-injectors for all patients at risk for food-induced anaphylaxis. . [Recommendation; B Evidence]

Summary Statement 33: Advise patients that avoidance of food allergens remains the mainstay of long-term treatment of food-induced anaphylaxis. [Strong Recommendation; C Evidence]

Summary Statement 34: Do not use immunotherapeutic treatments (desensitization) in clinical practice to prevent food-induced anaphylaxis owing to inadequate evidence for therapeutic benefit over risks of therapy. [Recommendation; A Evidence]

Food allergens are the most common cause of anaphylaxis outside the hospital setting (see parameter on food hypersensitivity). Anaphylaxis rates from foods might have increased because the prevalence of food allergy appears to have increased.

Any food can theoretically lead to food-induced anaphylaxis[1]; however, peanuts, tree nuts, fish, shellfish, milk, and egg are the most commonly incriminated foods in the United States.[2,9–11] Food-induced anaphylaxis can occur at the first known ingestion of the allergen.[12,13] Anaphylaxis from non-ingestion exposure, such as contact with intact skin or being close to an allergen, is uncommon.[14,15]

The timing of the onset of symptoms of food-induced anaphylaxis is similar to that of other forms of anaphylaxis; however, more delayed reactions can occur.[16] An exception is delayed anaphylaxis, with symptom onset hours after ingestion, caused by mammalian meats (eg, beef, pork, and deer) attributed to IgE reactivity against the carbohydrate moiety, alpha-gal. The route of sensitization to alpha-gal appears to be related to tick bites.[17–19] The diagnosis of food allergy is reviewed in the NIAID Exert Panel Guidelines and in the recently published Food Allergy Practice Parameter. Also see the Section VIII of this parameter on EIA.

During anaphylaxis, cutaneous manifestations are those most commonly seen. However, one cannot rely on cutaneous manifestations to make a diagnosis of anaphylaxis from foods. In addition, laboratory markers such as serum tryptase might not be elevated during food-induced anaphylaxis. The severity of the reaction to a food allergen is unpredictable and previous reactions do not reliably predict future severity.[20,21] This is likely due to patient-specific (eg, age, degree of sensitization, target organ reactivity, or comorbid diseases) and event-specific (eg, amount ingested, how the food was prepared, rate of absorption, concomitant viral illness, exercise, concomitant alcohol ingestion, or drug intake such as NSAIDs) variables.

Fatal and near-fatal food-induced anaphylaxis has been reported. At increased risk of such reactions are (1) adolescents and young adults, (2) patients with asthma, (3) patients on β-blocker medication, (4) patients who have a history of anaphylaxis without skin manifestations, (5) patients with a history of tree nut or peanut allergy, and (6) patients with a history of anaphylaxis. In addition to these general risk factors, the most consistent is the failure to promptly treat anaphylaxis with epinephrine, which puts the patient at risk of a fatal or near fatal reaction.[13,16,20,22–25]

The 2010 NIAID Food Allergy Guidelines recommend that all patients who have experienced, or at risk for, food-induced anaphylaxis be prescribed epinephrine auto-injectors. This includes patients with food allergy and asthma; patients allergic to peanut, tree nuts, fish, and shellfish; and patients with a history of an SR from food.[10] In addition, the expert panel suggests that consideration should be given to prescribing an epinephrine auto-injector to all patients with IgE-mediated food allergy. Patients and caregivers should be instructed on the use of the device and patients should have the device readily available at all times.[26–33]

Currently, avoidance of the food allergen remains the mainstay of treatment. Even with education and appropriate avoidance measures in place, accidental reactions are common, with reports suggesting that more than 50% of children will have a reaction within 36 months of observation.[34] To help minimize the risk of unintentional exposures, patients and parents should be educated on how to properly read and interpret product ingredient labels, avoid cross-contamination with their known allergen during food preparation, and inquire about exposure at restaurants.[10] Patients' understanding of possible food allergen exposure will increase the possibility of eating safely at restaurants. Patients also should wear medical identification jewelry.[10] Written emergency action plans can provide guidance for treatment of food-induced anaphylaxis.[10] Examples of action plans and educational material can be found at the following Web sites: http://www.foodallergy.org and http://www.cofargroup.org.[35]

During the past decade, multiple studies have examined the utility of desensitization regimens, mostly through the oral and sublingual routes, as a treatment for food allergy.[36] Most studies have suggested that these approaches achieve desensitization (an improved threshold with continuous dosing) for most patients, but it appears that relatively few patients attain tolerance (the ability to ingest the food after cessation of treatment dosing); and side effects of treatment are common and potentially severe.[37–40] Currently, this therapy remains investigational.[27]

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IV. Anaphylaxis to Drugs and Biological Agents

Summary Statement 35: Consider drug-induced vocal cord dysfunction if the patient presents with a history of throat tightness and swelling without visible orofacial angioedema and has been diagnosed as having anaphylaxis. [Strong Recommendation; D Evidence]

Summary Statement 36: Perform skin tests for the major (benzylpenicilloyl polylysine) and a minor determinant (penicillin G) of penicillin in patients who present with possible anaphylaxis to penicillin recognizing that the negative predictive value is 95% to 99%. [Strong Recommendation; B Evidence]

Summary Statement 37: Consider patients with a history of penicillin induced-anaphylaxis, especially if it is a remote history, to be at very low risk to react to cephalosporins, recognizing that life-threatening reactions have occurred when patients allergic to penicillin are given cephalosporins. [Strong Recommendation; B Evidence]

Summary Statement 38: Recognize that vancomycin can produce manifestations similar to anaphylaxis that are not mediated by IgE and can be prevented by slow infusion of the drug. [Strong Recommendation; C Evidence]

Summary Statement 39: Recognize that anaphylactic reactions to omalizumab can be delayed in onset and progressive. Therefore, observe patients for 2 hours after the first 3 injections and 30 minutes after subsequent injections. [Strong Recommendation; C Evidence]

Summary Statement 40: Because of the risk of anaphylaxis, prescribe an AIE for all patients receiving omalizumab and instruct patients in its use. Advised them to carry it before and 24 hours after their omalizumab injection. [Strong Recommendation; D Evidence]

Summary Statement 41: Consider skin testing for patients who have developed anaphylaxis from biologic agents. If patients have developed anaphylaxis to biologic agents and no therapeutic alternative exists, consider rapid desensitization to induce temporary tolerance, recognizing that repeat desensitizations might be necessary depending on the interval between infusions. [Strong Recommendation; C Evidence]

Summary Statement 42: Use a lower osmolality RCM and premedicate patients with prednisone and diphenhydramine if the patient has a history of anaphylactoid reactions to RCM. [Strong Recommendation; D Evidence]

Medications are the second most common overall cause of anaphylaxis and the primary cause of anaphylaxis in adults and of fatal anaphylaxis.[1,2] The most common classes of drugs producing

anaphylaxis are (1) antibiotics, especially β-lactam antibiotics, and (2) NSAIDs. Unfortunately, there are no adequate skin tests for demonstrating IgE-mediated (allergic or anaphylactic) potential to most drugs. Therefore, in most instances, the diagnosis of drug hypersensitivity is based on history.

It is important to recognize that patients with vocal cord dysfunction can present with histories suggestive of drug-induced anaphylaxis. These patients typically report a history of "anaphylaxis" and on further questioning report isolated "throat swelling" without other objective findings of anaphylaxis. Although some patients might report lip swelling, they lack objective findings of lip, tongue, or orofacial edema.[3] Most of these patients do not have histories of asthma and might not have other triggers for vocal cord dysfunction.

β-Lactam Antibiotics

The β-lactam antibiotics, including penicillin and cephalosporins, are not an uncommon cause of anaphylaxis.

Non–β-lactam antibiotics appear to be uncommon causes of anaphylactic reactions. Diagnosis of IgE-mediated allergy to these drugs is more difficult because of the lack of knowledge about relevant metabolites and allergenic determinants. Skin testing with the native antibiotic can yield some useful information. If a nonirritating concentration is used, then a positive result suggests the presence of drug-specific IgE antibodies.[4] It is important to recognize that a negative drug skin test result does not indicate lack of drug allergy because the negative predictive value for these tests is unknown.

Vancomycin is well known to cause nonspecific mast cell activation resulting in the "red man syndrome" characterized by pruritus, erythema and flushing of the face, neck, and upper chest with occasional hypotension. Differentiating vancomycin anaphylaxis from flushing and hypotension from nonspecific mast cell activation can be challenging and therefore skin testing with a nonirritating concentration of vancomycin should be considered.

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs, including cyclooxygenase-2–specific inhibitors, have been reported to produce anaphylactic reactions. NSAIDs are one of the most common causes of drug-induced anaphylaxis including severe anaphylaxis.[5,6] Anaphylactic reactions to NSAIDs are unrelated to other reactions caused by these drugs, such as respiratory reactions and exacerbations of chronic idiopathic urticaria. Although respiratory and urticarial reactions are often referred to as anaphylactic, efforts to detect drug-specific IgE antibodies (through skin testing or in vitro testing) have generally been unsuccessful in patients who experience these reactions. True anaphylactic reactions to NSAIDs appear to be specific to medication in that the vast majority of patients who have had an anaphylactic reaction to 1 NSAID can tolerate structurally unrelated NSAIDs.[7,8] Although aspirin is often reported as a common cause of anaphylaxis in the literature, there is a lack of data supporting aspirin as a true cause of anaphylaxis.[9]

Anticancer Chemotherapy Drugs

Anaphylaxis to anticancer chemotherapy drugs is being encountered more frequently particularly to platinum-containing drugs, such as cisplatinum and carboplatin, and taxanes, such as palclitaxel.[10] Skin testing to these agents could be helpful in determining whether sensitivity exists and at what dose to proceed with desensitization if this is necessary.[11] In patients with remote histories of anaphylaxis whose skin test reaction was negative to carboplatin, repeat sin testing is recommended owing to the high rate of conversion to a positive skin test reaction, thus indicating a need for desensitization.[12] In addition, acute anaphylactoid infusion reactions occur in up to 30% of patients treated at first exposure[13] for which rapid desensitization is possible.[14] In some instances, the solvent in which these drugs are formulated (Cremophor-L) might cause an anaphylactic reaction.[15] Components other than the drug product might be the cause of significant reactions with other drugs, such as heparin.[16]

Biological Modifiers and Monoclonal Antibodies

Anaphylaxis to biological modifiers and monoclonal antibodies has been known to occur.[17] Most notably, there has been concern regarding anaphylactic events that occurred after administration of omalizumab (anti-IgE). In this regard, 2 separate omalizumab joint task forces classified 18 of 101 potential cases and 77 of 127 potential cases as meeting criteria for anaphylaxis.[18,19] A significant proportion of anaphylactic reactions to omalizumab was delayed in onset and exhibited a protracted progression of symptoms. Some cases required hospitalization. No potential factors were noted that identified patients at risk for such reactions.

It has been recommended that (1) patients should be observed for 2 hours after the first 3 injections of omalizumab and for 30 minutes after subsequent injections; (2) omalizumab should not be administered at home or in a facility that does not have appropriate staff and equipment to treat anaphylaxis; (3) informed consent should be obtained after discussing the risks, benefits, and alternatives to treatment with omalizumab; (4) patients receiving omalizumab should be trained in the recognition of the signs and symptoms of anaphylaxis and in the use of an epinephrine auto-injector; (5) patients should be advised to have this auto-injector available during and after the administration of omalizumab; (6) the physician should ensure that patients have their injector and have been instructed in its use; and (7) an assessment of patients before the administration of omalizumab should be made, including vital signs, an assessment of asthma control, and a measurement of lung function.[18]

Cetuximab, a chimeric mouse and human IgG1 monoclonal antibody to epidermal growth factor receptor used in the treatment of colorectal cancer and squamous cell cancer of the head and neck, has been associated with anaphylactic reactions.[20] Anaphylaxis occurs because IgE antibodies develop to alpha-gal present on the Fab portion of the cetuximab heavy-chain. IgE antibodies also have been demonstrated to this galactose carbohydrate epitope in meat, which might account for reactions that occur during the first dose.[21] Anaphylaxis has been reported to many other biologics, and several case reports and case series have suggested that patients can be successfully desensitized after an allergic reaction.[22–28] Biologics have much larger molecular weights compared with most small drugs, which are haptens, and intradermal skin test reactions have been shown to be positive in most patients with allergic reactions to rituximab, infliximab, and trastuzumab who underwent desensitization.[28] Therefore, skin testing should be considered in the evaluation of patients with anaphylaxis to biologics. The negative predictive value of these skin tests is unknown and patients whose skin test reactions are negative can still have reactions during desensitization.

Radiographic Contrast Material

Radiographic contrast material is used in more than 10 million radiologic examinations annually in the United States. The overall frequency of adverse reactions (including anaphylactoid and nonanaphylactoid reactions) is 5% to 8%. Moderate reactions, such as severe vomiting, diffuse urticaria, or angioedema, that require therapy occur in approximately 1% of patients who receive RCM. However, life-threatening reactions occur with a frequency lower than 0.1% with conventional high-osmolality RCM.[29] Although studies quote a wide spectrum of mortality, a reasonable estimate is 1 in every 75,000 patients who receive RCM.[30] With the recent development of lower-

osmolality RCM, the overall risk of anaphylactoid reactions seems to have decreased to approximately one fifth that of conventional RCM.[31]

Patients who are at greatest risk for an anaphylactoid reaction to RCM are those who have experienced a previous anaphylactic reaction to RCM. This risk has been reported to be 16% to 44%.[32,33] Even without a history of a anaphylactoid reaction, patients with asthma, β-blockade, or cardiovascular disease are at greater risk of developing a more severe reaction.[34,35] There is no evidence that seafood or inorganic iodine levels present in seafood or in topically applied iodine-containing solutions are related to anaphylactoid events from RCM.[36]

Most anaphylactic reactions appear to be not mediated by IgE and are considered anaphylactoid reactions. Anaphylactoid reactions to RCM are independent of the dosage or concentration of RCM administered. Clinically, these reactions are identical to immediate hypersensitivity IgE-mediated reactions (anaphylaxis) but do not appear to involve IgE or any other immunologic mechanism.[32]

Pretreatment regimens for prevention of repeat anaphylactoid reactions have consisted of oral glucocorticosteroids, H_1 and H_2 antihistamines, and other medications such as ephedrine. The current recommendation of the JTF is 50 mg of prednisone given orally 13, 7, and 1 hours before administration of RCM and 50 mg of diphenhydramine given orally or intramuscularly 1 hour before the administration of RCM (see drug allergy parameter).[37] If the patient has to undergo an emergency radiographic procedure, an emergency pretreatment protocol that has been used successfully consists of 200 mg of hydrocortisone administered intravenously immediately and then every 4 hours until the RCM is administered and 50 mg of diphenhydramine administered intramuscularly 1 hour before RCM administration.[38]

Recently, IgE-mediated reactions to RCM have been reported based on positive skin or basophil activation test results. The prevalence of positive skin test results varies considerably in those with histories of immediate reactions and could be more frequent in those with more severe reactions.[39] The largest series is from a multicenter European trial that described 32 of 122 patients (26%) with immediate reactions after positive RCM skin test results.[40] Because the vast majority of patients with histories of immediate reactions to RCM tolerate subsequent RCM with the aforementioned premedication protocols, the clinical significance of these positive skin test reactions is unclear. In patients who have recurrent anaphylactoid reactions despite premedication, skin testing to RCM could be helpful in identifying a possible IgE-mediated reaction. The negative predictive value of these tests is unknown and drug challenges have indicated that patients can have false-negative skin test results.[41]

Drug Desensitization

In patients with IgE-mediated drug-induced anaphylaxis who require the causal drug and no equally efficacious alternative exists, drug desensitization should be considered to induce temporary drug tolerance. Drug desensitization procedures vary with individual drugs and they are intended for agents that induce IgE-mediated reactions and, in some cases, for anaphylactoid (non–IgE-mediated anaphylaxis) reactions (such as for paclitaxel and other chemotherapeutic agents). The duration of the procedure depends on the drug and route of administration but, in most cases, can be accomplished within 4 to 12 hours.[37,42] Drug desensitization should be performed in an appropriate setting, supervised by physicians familiar with the procedure, with continual monitoring of the patient and readiness to treat reactions including anaphylaxis should it occur. Protocols are available for different drugs including virtually all classes of antibiotics, insulin, chemotherapeutic agents, and biological agents such as humanized monoclonal antibodies.

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V. Insect Sting Anaphylaxis

Summary Statement 43: Do not generally perform in vitro or skin tests for specific IgE antibodies to venom or start VIT in patients who have large local reactions and in children with mild (cutaneous) SRs, because the chance of an SR to a sting is low (5–10%). These groups do not generally require venom testing or VIT. [Strong Recommendation; A Evidence]

Summary Statement 44: Consider obtaining a baseline serum tryptase level to rule out mastocytosis in patients with suspected anaphylactic reactions to stings. [Strong Recommendation; A Evidence]

Summary Statement 45: If patients need to be evaluated for stinging insect hypersensitivity, perform a venom skin test because it is the most sensitive diagnostic test, although in vitro testing is an important complementary test. [Strong Recommendation; A Evidence]

Summary Statement 46: Do not rely on the degree of sensitivity on skin or in vitro testing because it does not reliably predict the severity of a sting reaction. [Recommendation; B Evidence]

Summary Statement 47: Recognize that a diagnosis cannot be made on skin or serum testing alone and the history is essential, because asymptomatic venom sensitization can be detected in up to 25% of adults. [Strong Recommendation; B Evidence]

Summary Statement 48: Recommend VIT for patients with systemic sensitivity to stinging insects because this treatment is highly (80–98%) effective. [Strong Recommendation; A Evidence]

Summary Statement 49: Diagnose and treat allergy to fire ant stings with whole-body extracts, which provide adequate allergen concentrations for reasonable efficacy. [Recommendation; B Evidence]

Stinging insects of the order Hymenoptera can cause systemic allergic reactions including anaphylaxis, but biting insects rarely cause such reactions. Large local sting reactions can cause delayed and prolonged local inflammation increasing over 24 to 48 hours and resolving in 3 to 10 days. These reactions are mediated by IgE but carry a relatively low risk of anaphylaxis from future stings.[1] Systemic (generalized) reactions can include at least 1 of the signs and symptoms of anaphylaxis.[2,3] SRs involving only cutaneous manifestations must be considered in the diagnosis and treatment of stinging insect allergy as potential precursors of anaphylactic reactions. Anaphylaxis from an insect sting differs clinically between children and adults. Systemic allergic reactions to insect stings are reported by up to 3% of adults and almost 1% of children.[4–6] At least 50 fatal reactions to an insect sting occur each year in the United States. Half of these occur in individuals who had no history of reaction to an insect sting.[7,8] Screening for clinically significant hymenoptera sensitivity is complicated by the fact that up to 25% of adults and more than 30% of those stung in the previous 3 months have venom-specific IgE by skin or in vitro testing, although most had no history of an allergic reaction to an insect sting.[5] Although many of these individuals exhibited negativity to venom-specific IgE after 3 to 6 years, those whose positivity remained had a 17% frequency of an SR to a subsequent sting.[9]

Toxic reactions owing to massive envenomation from multiple stings estimated to be more than 100 might be clinically indistinguishable from allergic reactions because mediators can produce physiologic effects that mimic those produced from an allergic reaction.[10]

Clinical features of anaphylaxis from an insect sting are identical to those from other causes of anaphylaxis. If the patient experiences a large local reaction to an insect sting, in the absence of a systemic response, then VIT is not usually necessary, although patients with large local reactions are at slightly increased risk for an SR (5–10%). In children, an SR consisting of urticaria alone does not always mandate VIT. In prospective sting challenge studies in adults, fewer than 1% of patients had a reaction more severe than their previous reaction,[11,12] although in retrospective surveys more severe reactions were noted in a larger percentage of patients.[13,14] Life-threatening reactions are estimated to occur in fewer than 3% of such patients.[15–17]

Recurrence rates of reactions in adults vary from 25% to 70% depending on the severity of the previous systemic sting reaction. Patients with a history of an anaphylactic reaction to an insect sting should have a measurement of serum tryptase to rule out mast cell disease.

Individuals who are allergic to stinging insects should avoid areas with a high risk of exposure, particularly outdoor settings with foods and drinks that can attract stinging insects. However, excessive fear can impair a patient's quality of life and needs to be included in the considerations for VIT.[18] Auto-injectable epinephrine should be provided to any patient who has experienced an SR to an insect sting, with the possible exception of children who have experienced only a cutaneous reaction. Patients discharged from emergency care of anaphylaxis should be given or prescribed AIE and receive instruction in its proper use and indications for use and advised to set up an appointment with an allergist or immunologist. However, patients should understand that they should seek emergency medical attention in conjunction with using AIE; auto-injectors are not a substitute for emergency medical attention.

Diagnostic tests are indicated in patients who have had SRs to insect stings.[16,19] The preferred diagnostic method is venom skin testing because of its high degree of sensitivity and proven safety,[16,20] but in vitro testing is an important complementary test. The degree of sensitivity on skin or in vitro tests does not reliably predict the severity of a sting reaction. Because asymptomatic venom sensitization can be detected in up to 25% of adults, diagnosis cannot be made on skin or serum testing alone; the history is essential. Skin test results are positive in 65% to 85% of patients with a convincing history of SR. Venom skin tests also show unexplained variability over time so that test results can be negative on one occasion and positive on another.[21]

A negative skin test reaction in a history-positive patient can be due to loss of sensitivity over time. In addition, there is a refractory period of several weeks after an insect sting reaction, during which a false negative skin test reaction can occur. In this situation, skin tests might have to be repeated after 1 to 6 months.[22] The degree of skin test sensitivity does not correlate reliably with the severity of a sting reaction. In vitro testing is less sensitive than skin testing but might be useful when skin tests cannot be done or when skin test results are negative in a patient with a history of an SR.[20]

Some investigators have suggested that sting challenge is the most specific diagnostic test, but others have found this unethical and impractical.[12,23,24] Furthermore, a single negative sting challenge result does not preclude anaphylaxis to a subsequent sting.[11,25]

In placebo-controlled trials, VIT was 80% to 98% effective in completely preventing SRs to stings.[26–28] The indications for VIT are a history of a systemic allergic reaction to a sting and a positive diagnostic test reaction for venom-specific IgE. Those with a recent history of anaphylaxis from an insect sting and a positive skin test reaction have a 30% to 70% chance of an SR to a subsequent sting.[12,27,29] VIT is not required when the chance of an SR is less than 10%, as in large local reactors and children with cutaneous-only SRs, but still can be considered in this setting.[15,17,30]

Therapy is 98% effective in completely preventing a systemic allergic reaction to a sting when treatment includes mixed vespid venoms (300 μg total dose), but complete protection is achieved in only 75% to 90% of patients using 100 μg of any single venom (eg, honeybee, yellow jacket or Polistes wasp).[31–33] Fire ant immunotherapy using whole-body extracts has been reported to be reasonably safe and effective, although no controlled studies have been performed.[34–36] Fire ant venoms are not available for diagnosis or treatment, but there has been a very successful controlled trial of immunotherapy with Jack Jumper ant venom in Australia.[26]

Protection from sting anaphylaxis with rapid venom immunotherapy can be achieved in days or weeks, and adverse reactions are no more common than with regular inhalant therapy.[36–38]

Most patients can discontinue VIT after 5 years with low residual risk (<5%) of a severe sting reaction. VIT should be continued beyond 5 years when there are high-risk factors such as extreme or near-fatal reaction to sting before VIT, elevated baseline serum tryptase, SR during VIT, and honeybee allergy. There is a need to develop tests that are (1) markers of susceptibility and can serve as screening tests to identify patients at high risk of sting anaphylaxis and (2) markers of tolerance induction to identify patients who can safely discontinue VIT.

The risk of β-blocker or ACE inhibitor medications during VIT remains controversial. In a large multicenter retrospective study of patients with insect sting allergy, the use of these antihypertensive medications was associated with an increased frequency of severe anaphylaxis.[39] However, in another large study of more than 600 patients with insect allergy, there was no increased risk of reaction in patients on either type of antihypertensive medication.[40] Because antihypertensive medications are frequently prescribed for patients with cardiovascular disease, one interpretation of these data is that use of these medications is a marker for patients with more severe cardiovascular disease. Conversely, because β-blockers and ACE inhibitors can enhance risk for more severe anaphylaxis based on previously published case reports,[41] it is prudent to consider suspension or replacement, whenever feasible, of β-blockers or ACE inhibitors to lower the risk for untoward outcomes in patients with anaphylactic potential to hymenoptera venom and/or receiving VIT. For patients who require β-blockers or ACE inhibitors for an indication for which there is no equally effective alternative available, a management decision by the physician prescribing VIT should be approached cautiously on an individualized risk-vs-benefit basis.[16]

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VI. Perioperative Anaphylaxis: Anaphylaxis before, during, or Immediately after Anesthesia

Summary Statement 50: Recognize that perioperative anaphylaxis has greater morbidity and mortality than other forms of anaphylaxis. [Strong Recommendation; B Evidence]

Summary Statement 51: Recognize that anaphylaxis during the perioperative period is difficult to diagnose because of the inability of the affected patient to communicate, the decreased occurrence of skin manifestations in perioperative anaphylaxis, and the number of medications administered simultaneously. [Strong Recommendation; B Evidence]

Summary Statement 52: Perform skin testing for suspected reactions to neuromuscular blocking agents, β-lactam antibiotics, and barbiturates. [Recommendation; C Evidence]

Summary Statement 53: Consider in the evaluation of perioperative anaphylaxis medications (opioids, neuromuscular agents, antibiotics, etc) blood transfusions, supravital dyes, and latex. [Strong Recommendation; B Evidence]

Summary Statement 54: Recognize that pretreatment with antihistamines and corticosteroids may not prevent perioperative anaphylactic events. [Recommendation; C Evidence]

The incidence of anaphylaxis related to anesthesia is not precisely known. Clinical experience suggests that anaphylaxis is more common with general anesthesia than with local or spinal anesthesia. The anaphylaxis incidence with general anesthesia varies from 1:10,000 to 1:20,000, with the variability attributed to difficulties in determining the total number of anesthetics administered and the limitations in diagnosing or recognizing peri-anesthetic anaphylaxis.[1–4] Perioperative anaphylaxis is more common in women but is equal between boys and girls.[3] The challenges with recognition of perioperative anaphylaxis include the decreased occurrence of skin manifestations, multiple physiologic changes occurring during surgery that could mask or emulate anaphylaxis, surgical draping covering the skin and limiting recognition of urticaria or flushing, and inability of the anesthetized patient to verbalize symptoms.

The severity of perioperative anaphylaxis is greater than anaphylaxis in general, with estimated mortality ranging from 1.4% to 6%, with another 2% experiencing the morbidity of brain damage.[5–7] The explanation for the increase in risk is not known but could be a result of more rapid exposure to culprit medications owing to frequent intravenous medication administration, delay in recognition and treatment of anaphylaxis, and possibly increased vulnerability of the affected patient owing to physiologic changes of surgery. IgE-mediated anaphylaxis is more severe than anaphylaxis from other mechanisms.[3]

The pathogenetic mechanisms of perioperative anaphylaxis are multiple and include nonimmunologic direct mast cell and basophil degranulation (eg, RCM, opioids, and some neuromuscular blocking agents), IgE-mediated anaphylaxis (eg, antibiotics and latex), and immunologic non–IgE-mediated anaphylaxis from immune complexes activating complements (eg, blood transfusion).

Antibiotics are likely the most common cause of perioperative anaphylaxis in the United States (approximately 50% of cases), whereas neuromuscular blocking agents are the most common suspected etiology in Europe (approximately 70% of cases).[8,9] The proof of cause is based on the timing of medications given, the onset of anaphylaxis, and the detection of specific IgE, because challenge with culprit drugs is difficult, particularly with general anesthetic drugs. The development of specific IgE to potential etiologic agents can result from prior exposure to the culprit agent, cross-reactions with food (eg, latex), and cross-reactions with other medications (eg, neuromuscular blocking agents).

Testing for specific IgE is helpful if IgE-mediated anaphylaxis is suspected, although few culprit drugs have reliable or standardized testing available. Estimates suggest that 60% of perioperative anaphylaxis is due to specific IgE.[5] Latex in vitro IgE testing is available in the United States, and an approved latex skin testing reagent is available in Canada.[2,3,10,11] IgE testing for penicillin and some other β-lactam antibiotics is supported by large datasets. Testing for specific-IgE for all the other possible causes of perioperative anaphylaxis is based on limited information.[12,13] In addition to antibiotics and latex, a probable IgE-mediated mechanism is likely for anaphylaxis after exposure to neuromuscular blocking drugs, protamine,[14,15] chlorhexidine,[16–20] blood transfusions containing IgA in IgA-deficient patients, barbiturates,[10,21–25] and isosulfan blue and other supravital dyes used for lymph node dissection.[26–28]

The diagnosis is difficult for several reasons. The patient is often unable to communicate. Skin manifestations are less common with peri-anesthetic anaphylaxis compared with other types of anaphylaxis and surgical drapes often obscure the visibility of the skin. Also, the multiple physiologic changes that occur from various medications and the effects of surgery can delay the recognition of an anaphylactic event. Therefore, obtaining a blood sample of serum tryptase should be considered at this time if possible.

The causes of perioperative anaphylaxis and the mechanisms are varied (Table VI-1). The most common causes are reactions to antibiotics or neuromuscular blocking agents.[8,9]

Anaphylaxis occurring within the first 30 minutes of surgery is more likely due to antibiotics, neuromuscular blocking agents, or hypnotic inducing agents. Anaphylaxis with onset after 30 minutes of anesthesia is more likely due to latex, protamine, supravital dyes, plasma expanders, or blood transfusion.[2]

Serum tryptase was increased in 68% of IgE-dependent peri-anesthetic anaphylaxis cases in a large French study, whereas only 4% of non–IgE-dependent reactions were associated with increased tryptase.[3]

Neuromuscular blocking agents can cause IgE-independent and IgE-dependent anaphylaxis.[23] The tertiary or quaternary ammonium structure common to all neuromuscular blocking agents is likely responsible for the cross-reactivity among agents and the occurrence of reactions at the first administration.[29–38] The cross-reactivity also could result in falsely positive skin test results for IgE to neuromuscular blocking agents, resulting in the incorrect attribution of the anaphylaxis to the neuromuscular blocking agent, which is usually not confirmed by challenge. Other pharmaceuticals that can cross-react with neuromuscular blocking agents include the cough suppressant pholcodine, acetylcholine, choline, morphine, neostigmine, and pentolinium. Three of 4

neuromuscular blocking agent reactions occur in women, suggesting that cross-reactions with ammonium compounds in makeup and other personal care products could be responsible.[22] Skin testing is unlikely to be useful in selecting the safest alternative for subsequent surgery because of the unknown predictive value.[33,39]

Antibiotics are responsible for more than 50% of anaphylaxis episodes related to anesthesia and surgery in the United States and 12% to 15% in France.[3,9,10] Most reactions are to β-lactam antibiotics or vancomycin (see Section IV, Anaphylaxis to Drugs and Biological Agents). The β-lactam antibiotic reactions are usually due to specific IgE. Vancomycin can cause direct mediator release from mast cells and IgE-mediated events.[2,10,40]

Latex or natural rubber latex was the etiology of 20% of perioperative anaphylaxis in previous studies.[2,3,10] The occurrence is decreasing owing to increased vigilance and the decrease in the use of latex products in operative suites. The most common sources of significant latex exposure in the perioperative setting are sterile examination gloves, drains, and urinary catheters (Table VI-2). Hard rubber items, such as straps, tubing, and blood pressure cuffs, elute little or no latex protein and do not contact patient tissues to the same extent. Items that are currently usually free of latex include Ambu-bags, catheter leg bag straps, bandages and adhesive pads, tape, electrode pads, endotracheal tubes, infusion sets and ports, and suction catheters. Latex allergy is more likely in patients with repeated exposure to latex gloves or catheters from prior surgeries or from occupational use, especially children with spina bifida and health care workers.[11] Sensitization to latex can occur as a result of contact with nonmedical sources of latex (eg, condoms, balloons, and household gloves) and reactions are not limited to patients in high-risk groups.

Narcotics when administered intravenously will commonly cause flushing and urticaria and could cause anaphylactoid reactions.[41–43] Dermal mast cells express opioid receptors that stimulate mediator release without specific IgE. Fentanyl does not interact with the mast cell opioid receptor.[45] Lowering the rate of administration generally lessens the severity of adverse effects. There are rare reports of IgE-mediated anaphylaxis to morphine and fentanyl.[44–46] Skin testing with narcotics is of limited value owing to the potential of nonspecific histamine release and the unknown predictive value. Fentanyl is less likely to produce a false positive skin test than other opioids.[47]

Induction agents are responsible for no more than 2% of anaphylaxis episodes related to anesthesia.[3] Induction agents responsible for anaphylaxis are generally barbiturates such as phenobarbital or methohexital. Barbiturates generally cause IgE-dependent reactions. Women are affected 3 times more often than men.[1,10] There is some cross-reactivity among the different barbiturates. The nonbarbiturate induction agents, such as benzodiazepines, propofol, etomidate and ketamine, do not generally cause reaction. Propofol was previously solubilized in a castor oil vehicle that resulted in anaphylaxis. Currently, propofol is administered in a soybean emulsion with egg phosphatide.[48–50] Allergic reactions to this newer preparation are extremely rare, although allergies to egg or soybean are listed as contraindications in the package insert.[51]

Plasma expanders, such as dextran and hydroxyethyl starch, are used as fluid replacement instead of blood. Hydroxyethyl starch is generally used in major trauma, particularly when access to blood is limited. Anaphylaxis can occur in fewer than 0.1% of administrations.[22,52,53] Gelatin-containing plasma expanders are used in other parts of the world and sensitivity to gelatin has resulted in anaphylaxis.[54,55]

Blood transfusions can result in anaphylactoid reactions. This is generally mediated by IgG specific for a component within the transudate, including red blood cell mismatch. The result is complement activation with formation of anaphylatoxins C3a and C5a. IgA contained in the transfused blood also can cause a reaction if the recipient is deficient in IgA. The role of anti-IgA antibodies as a cause of γ-globulin–induced anaphylaxis in IgA-deficient patients is controversial. IgA deficiency is not a contraindication to IgG infusion, and skin testing to γ-globulin in IgA-deficient patients is not required in these patients. In addition, transfusion-related acute lung injury can resemble anaphylaxis with hypotension, hypoxia, and shortness of breath up to 6 hours after transfusion.[56] Transfusion-related acute lung injury is responsible for up to 30% of transfusion-related deaths.

Protamine, an agent used to reverse heparin anticoagulation, can cause IgE-dependent and IgE-independent anaphylaxis.[56–61] Predisposing factors in some studies for a reaction to protamine include prior use of Hagedorn insulin (odds ratio 8.18, confidence interval 2.08–32.2), fish allergy (odds ratio 24.5, confidence interval 1.24–482.3), or other medication allergy (odds ratio 2.97, confidence interval 1.25–7.07).[60] However, other studies have found that allergy to fish is not associated with reactions to protamine.[61,62] Neither skin testing nor in vitro testing of IgE specific for protamine is available.

Chlorhexidine, an antiseptic commonly used in dental rinses, surgical scrubs, and sterilizing solutions, can cause anaphylaxis. Skin testing with chlorhexidine (0.5% chlorhexidine digluconate solution for prick-and-puncture skin testing, 0.0002% for intradermal testing) shows positivity in at least some of these cases, suggesting that chlorhexidine might be an important immunologic cause of perioperative anaphylaxis.[63,64] The predictive value of skin testing for chlorhexidine has not been determined.

Isosulfan blue, a supravital dye (ie, capable of staining live cells), and other aniline dyes, such as methylene blue, are used to identify sentinel lymph nodes that are associated with specific anatomic areas with confirmed or suspected malignancy. This technique is used especially with breast cancer. Isosulfan blue has a warning in the package insert of a risk of anaphylaxis of 1% to 3%, and sustained and biphasic reactions have been described.[65] The risk of anaphylaxis is probably similar with the chemically related supravital dye patent blue V and lower with methylene blue.[27,65–70]

The safest approach for managing future anesthesia in a patient who developed perioperative anaphylaxis is avoidance of the culprit agent. Therefore, every effort should be made to identify the responsible trigger, so that the patient is not restricted to receiving multiple second-line agents. Unfortunately, even a very thorough evaluation might show no evidence of allergy to a specific agent. In these cases, future management involves avoidance of high-risk agents and adherence to the general precautions discussed below. In other evaluations, a positive skin test result might be obtained to more than 1 agent, raising the possibility that at least 1 result is falsely positive with regard to causality because the predictive value of these agents is not known; this is a particular concern with neuromuscular blocking agents or opioids. Future use of alternative neuromuscular blocking agents with negative skin test results appears to be safe.

For any patient with a history of perioperative anaphylaxis, there are several general precautions that should be applied to future procedures requiring anesthesia. (1) Asthma should be as well controlled as possible before receiving anesthesia. (2) Avoid β-blockers if possible, especially if the culprit agent could not be conclusively identified. Beta-blockers can increase the severity of anaphylaxis and decrease responsiveness to epinephrine. However, some patients might have cardiovascular conditions for which β-blockade is critical, and these cases require multidisciplinary consideration. (3) Consider avoidance of ACE inhibitors because they can interfere with compensatory physiologic responses to anaphylaxis and exaggerate bradykinin-induced vascular changes, although these data are not robust. Recognize that the decision to discontinue these medications before repeat anesthesia must be

Table VI-1
Agents frequently implicated in perioperative anaphylaxis and probable mechanisms of adverse reactions

Agent	IgE-mediated mast cell activation	Complement-mediated mast cell activation	Direct mast cell activation
Muscle relaxants d-tubocurarine	+	−	+
Suxamethonium (succinylcholine)			
Pancuronium			
Atracurium			
Vecuronium			
Hypnotics and barbiturates	+	+	+
Thiopental			
Methohexitone			
Nonbarbiturate hypnotics	±	+	+
Propofol			
Althesin			
Opioids	±	−	+
Morphine			
Buprenorphine			
Fentanyl			
Plasma expanders	−	+	+
Dextran			
Hydroxyethyl starch			
Protamine	+	+	+
Radiocontrast media	−	+	+
Latex	+	−	−
Chlorhexidine	+		
Supravital dyes	+		

individualized depending on the severity of the reaction and on whether a specific cause could be implicated. (4) Infuse drugs that can cause direct release of histamine from mast cells and basophils (eg, morphine, vancomycin, and quaternary neuromuscular blocking agents) as slowly as possible, particularly if they are being infused in close temporal proximity. Use drugs that do not have these properties, if available. (5) Antibiotics should be administered slowly, with careful hemodynamic monitoring. Loading or initial doses should be given before induction of anesthesia, while the patient is awake, whenever possible, and not concomitantly with multiple other anesthetic agents. (6) Verify that baseline total serum tryptase is not elevated. Recognize that doing so could be helpful in identifying patients at increased risk of anaphylaxis owing to clonal mast cell disorders (>11 ng/mL) or mastocytosis (>20 ng/mL). Additional precautions should be implemented in such individuals because they are at increased risk of anaphylaxis in general.

Table VI-2
Latex-containing articles potentially used for anesthesia or surgery

Adhesive tape
Airway masks
Ambu-bag
Anesthesia bags and tubing
Self-adhesive bandages
Blood pressure cuffs
Bulb syringes
Catheter leg bag straps
Catheters
Condoms
Indwelling
Straight
Elastic bandages
Electrode pads
Endotracheal tubes
Gloves, sterile and exam
Intravenous bags, ports, infusion sets
Penrose drains
Rubber pads
Stethoscope tubing
Suction catheters
Syringes
Tourniquets

Alternative forms of anesthesia have the potential advantage of avoiding the use of neuromuscular blocking agents and hypnotic induction agents. In addition, patients are breathing spontaneously and are awake and can communicate symptoms, such as pruritus or dyspnea. However, these forms of anesthesia might not be appropriate for many types of surgery.

Local anesthesia or nerve blocks might be adequate in some situations. If the patient has a history of reacting to local anesthetic agents, then skin testing and challenge can be performed in advance of the administration of drug that will be used. Spinal or epidural anesthesia can be used for relatively minor surgeries below the diaphragm, although perioperative anaphylaxis has been reported in patients receiving these forms of anesthesia. The rate of recurrent reactions in patients who initially reacted during general anesthesia and later received spinal anesthesia is unstudied. In addition, the clinician should be mindful that the patient is essentially sympathectomized (below the level at which the anesthesia is introduced), lowering the baseline blood pressure and decreasing responsiveness to epinephrine and other sympathomimetic agents that would be needed if anaphylaxis were to recur. This is of particular concern in cases in which a culprit drug could not be identified. Thus, the general precautions noted earlier must still be applied when patients receive spinal anesthesia.

The evaluation of perioperative anaphylaxis involves a clinical history, detailed review of records of the event, and review of any tests for mast cell mediators that were obtained at the time. If an

Table VI-3
Skin testing concentrations for anesthetic agents

Medication	Intradermal skin test concentration (mg/mL)
Alcuronium	0.005
Methohexital	0.1
Metocurine	0.002
Pancuronium	0.002
Succinylcholine	0.02, 0.05
Thio amyl	0.1
Thiopental	0.20
Tubocurarine	0.0003, 0.001
Rocuronium	0.01
Vecuronium	0.004

IgE-mediated reaction is suspected or likely, skin testing or in vitro testing for allergen-specific IgE should be considered, recognizing that the predictive value of skin tests for most medications is not known. Suggested concentrations for skin testing to selected drugs used during anesthesia are listed in Table VI-3. IgE-mediated reactions are most common with neuromuscular blocking agents (muscle relaxants), latex, antibiotics (particularly penicillins and cephalosporins), isosulfan blue, and barbiturate induction agents. Skin tests can be performed for each of these agents, although commercial preparations for latex are not currently available in the United States. Skin testing should be performed by allergy specialists. In vitro tests for allergen-specific IgE are available for latex and a very limited number of other agents (eg, penicillin). In vitro testing is generally less sensitive than skin testing and the predictive value is not known. Perioperative anaphylaxis can result from at least 1 immunologic mechanism, and it is important to understand which mechanisms are associated with each specific agent and what type of testing is relevant (Table VI-1). The safest management approach for a patient with previous anaphylaxis is the definitive identification and complete avoidance of the trigger. Frequently, this is not possible or evaluation does not disclose a specific culprit; thus, future management must be based on avoidance of high-risk agents and implementation of general precautions. For patients who require repeat anesthesia, general precautionary measures include optimal preoperative control of asthma, slow administration of antibiotics and other high-risk agents, and avoidance (when possible) of β-blockers, ACE inhibitors, and drugs that cause direct histamine release from mast cells or basophils. Spinal or epidural anesthesia could be an option.

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VII. Seminal Fluid Anaphylaxis

Summary Statement 55: Diagnose seminal plasma anaphylaxis by skin testing with fresh whole human seminal plasma or its fractions obtained from the male partner. Exclude other underlying causes such as allergens in natural rubber latex condoms or in drugs or foods passively transferred through seminal plasma. [Recommendation; D Evidence]

Summary Statement 56: Treat patients with postcoital local reactions to human seminal plasma with intravaginal graded challenge to dilutions of whole seminal fluid or systemic desensitization to relevant seminal plasma proteins. [Recommendation; C Evidence]

Summary Statement 57: Instruct women with systemic seminal plasma hypersensitivity to have AIE readily available in the event of possible barrier failure with condoms occurs [Strong Recommendation; C Evidence]

Summary Statement 58: Perform intravaginal graded challenge with whole seminal plasma of the male partner, recognizing that the duration of protection is unknown, before pursing desensitization using relevant seminal plasma protein fractions in any patient who is likely to have had an IgE-mediated reaction to seminal plasma. [Recommendation; C Evidence]

Summary Statement 59: Perform desensitization using relevant seminal plasma protein fractions in patients who are likely to have had an IgE-mediated reaction to seminal plasma. [Recommendation; C Evidence]

Summary Statement 60: Inform patients with seminal plasma allergy that they might be able to conceive by artificial insemination with washed spermatozoa and that infertility does not appear to be linked to localized or systemic seminal plasma hypersensitivity. [Recommendation; C Evidence]

Coital anaphylaxis caused by human seminal fluid has been shown to be a result of IgE-mediated sensitization to seminal plasma proteins of varying molecular weight. Postcoital local reactions to human seminal plasma are probably mediated by IgE based on the successful response to rapid seminal plasma desensitization. A history of atopic disease is the most consistent risk factor for seminal fluid–induced anaphylaxis. The diagnosis of seminal plasma anaphylaxis can be confirmed by skin testing with fresh whole human seminal plasma or its fractions obtained from the male partner. It is essential to exclude other underlying causes such as allergens in natural rubber latex condoms or in drugs or foods passively transferred through seminal plasma. Prostate-specific antigen has been demonstrated to be a relevant allergen in some cases. Systemic and localized reactions to seminal plasma can be prevented by correct use of condoms. Nevertheless, in the event of barrier failure, sexual partners should be prepared to treat acute anaphylaxis. SCIT to properly prepared fractions of seminal plasma collected from male partners has been successful in preventing anaphylaxis to seminal plasma. Successful intravaginal desensitization with whole seminal plasma of the male partner has been reported in several cases, but the duration of protection is unknown. Patients with seminal plasma allergy might be able to conceive without undergoing desensitization by using artificial insemination with washed spermatozoa. Infertility does not appear to be directly linked to localized or systemic seminal plasma hypersensitivity.

Anaphylaxis owing to coital exposure to human seminal fluid is likely more common than previously reported.[1] Since the initial report in 1958,[2] approximately 30 cases of seminal fluid–induced anaphylaxis have been described.[3,4] All reactions have occurred in female patients during or after sexual intercourse. The vast majority of such reactions are caused by IgE-mediated sensitization to human seminal plasma proteins with molecular weights ranging from 12 to 75 kDa.[5–7] In rare cases, spermatozoa have been identified as the source of allergens, inducing a cell-mediated reaction.[8] Coital anaphylaxis also has been attributed to exogenous allergens transferred through semen during sexual intercourse. Such unusual reactions occur when a male partner ingests a food (eg, walnuts) or drug (eg, penicillin) to which there is established sensitization in the female partner.[9]

Seminal plasma hypersensitivity is essentially a diagnosis by exclusion. A detailed history is essential to rule out other causes, such as sexually transmitted diseases, latex sensitivity, or transfer of food or drug proteins from the male sexual partner to the female who might be sensitized to these agents or other contactants such as sanitary napkins. Anaphylaxis to seminal plasma protein begins within seconds to minutes after ejaculation and presents with a range of symptoms, including diffuse pruritus and urticaria; pelvic pain associated with uterine contractions; nasal symptoms including rhinorrhea and sneezing; wheezing, dyspnea, and/or laryngeal edema; and, rarely, hypotension and syncope. The effective prevention of reactions by correct use of condoms is a common feature.[4] Failure of condoms to prevent anaphylaxis suggests incorrect condom technique or concurrent sensitization to latex.[10] Localized vulvar and vaginal burning can occur as isolated symptoms or in conjunction with itching and swelling after ejaculation.[11] There is no evidence that localized vaginal seminal plasma hypersensitivity increases the likelihood of future SRs.

The most significant risk factor for seminal plasma protein anaphylaxis is a history of allergic asthma or atopic dermatitis.[3,7,12] Anecdotal case reports of seminal fluid anaphylaxis have occurred after birth, after gynecologic surgery, and after injection of anti-Rh immune globulin.[3] It has not been established whether such events are coincidental or could somehow modulate immune tolerance resulting in sensitization to seminal fluid proteins. Reactions also have been observed in women whose male partners have recently undergone prostatectomy or vasectomy.[13] Anaphylactic events

have been reported in women with multiple previous sexual encounters or in others after the first coital act.[3] Postcoital allergic reactions are not specific to 1 partner and almost always recur with different male partners. Surveys have indicated that most patients with seminal plasma hypersensitivity are not promiscuous, typically having reported a history of fewer than 2 sexual partners.[3] Cross-reactivity between human and dog prostate-specific antigen have led to speculation that cross-reactivity of proteins from dog epithelium and human seminal plasma results in seminal plasma hypersensitivity, but this has not been confirmed.[1,14]

The diagnosis must be confirmed by in vivo and/or in vitro demonstration of sensitization to seminal fluid proteins.[5] Based on available data, in vitro tests (eg, radioallergosorbent test or enzyme-linked immunosorbent assay) of serum specific IgE appear to be less sensitive than skin testing.[3] A negative serologic test result for seminal plasma specific IgE does not exclude sensitization. Therefore, skin prick testing with whole human seminal plasma from the male partner is recommended for initial screening of suspect cases. Before skin testing, the male donor must be screened for viral hepatitis, syphilis, and human immunodeficiency viral infection; if there is evidence of such infection, then skin testing should not be performed.[5,7,8]

Percutaneous or intracutaneous responses to relevant seminal plasma protein fractions have been detected in all reported cases of anaphylaxis. The presence of positive serologic specific IgE antibodies to these fractions and specific skin test reactions to the same fractions are strongly predictive of a successful treatment outcome with seminal plasma protein desensitization.[15]

Consideration must be given to the psychologic impact of this condition on the patient, the patient's partner, and the future of their relationship. Couples should be informed that successful pregnancies have been achieved after artificial insemination with sperm washed free of seminal plasma or by in utero fertilization.[13] Infertility does not appear to be linked to localized or systemic seminal plasma hypersensitivity.[16,17] Once the diagnosis is suspected, the patient must be advised to avoid coital exposure to seminal fluid. This can be achieved by temporary cessation of intercourse or with the correct use of condoms. Coitus interruptus is often not successful due to potential leakage of seminal fluid during intercourse, which can result in a reaction and is therefore discouraged. Condoms made from lambskin or a plastic polymer can be substituted in the latex-sensitive patient. If anaphylaxis is caused by seminal transfer of exogenous allergens, then the male partner should avoid the causative drug before engaging in sexual intercourse.[8,9] It is essential that patients and their partners be trained in the emergency use of AIE. Although there are reports of successful use of pre-coital treatment with antihistamines or intravaginal cromolyn sodium, these options have generally been ineffective in the prevention of anaphylaxis.[15]

There are couples for whom abstinence, regular use of condoms, or artificial insemination to achieve pregnancy are unacceptable options. In such situations, immunotherapy with seminal plasma fractions of the male partner should be considered. This procedure should be performed only in specialized centers and under the supervision of experienced physicians.[4–8,18]

Successful intravaginal desensitization has been reported in women diagnosed with human seminal plasma anaphylaxis confirmed by skin prick test reactivity to whole seminal plasma.[19–24] This approach is advocated as the first treatment approach because it is less costly and easier to perform because it does not require fractionation of the seminal plasma by chromatography as is done with parenteral desensitization protocols. The efficacy of intravaginal desensitization is based entirely on anecdotal reports. Moreover, the duration of the protective effect is unknown, but clinical experience suggests that the therapeutic response is sustained (D). Intravaginal desensitization has been less effective in women with localized seminal plasma hypersensitivity reactions.[25]

In summary, the following techniques can be used in the management of patients with seminal fluid induced anaphylaxis:

- Barrier condoms can be successful tools of management. In the patient with latex allergy, polyurethane condoms can be used.
- In cases of transfer of exogenous allergens, the male partner should avoid the food or drug in question.
- The patient with systemic seminal plasma hypersensitivity should be supplied with and trained in the use of an automatic epinephrine injector.
- When these therapies are not effective or are unacceptable, intravaginal desensitization to dilutions of whole seminal fluid followed by SCIT to relevant fractions of whole seminal fluid can be instituted.

It is very important to inform women with this condition that although seminal plasma hypersensitivity can cause significant stress, it has no impact on their ability to become pregnant because it has not been associated with infertility.[16,23,25]

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VIII. Exercise-induced Anaphylaxis

Summary Statement 61: Recognize that some patients experience anaphylaxis only if other cofactors are present in association with exercise. These "co-triggers" include ingestion of foods (specific or general), NSAIDs, especially aspirin, and rarely high pollen levels. [Strong Recommendation; C Evidence]

Summary Statement 62: Avoid exercise in the immediate postprandial period especially if EIA episodes are associated with the ingestion of food (food in general or a specific food). [Strong Recommendation; C Evidence]

Summary Statement 63: Recognize that identification of potential co-triggers is a critical component of the clinical history. Evaluate the patient for sensitization to relevant food allergens (history driven). [Recommendation; C Evidence]

Summary Statement 64: Recognize that exercise challenge testing does not consistently reproduce symptoms and is not a useful part of the evaluation. [Recommendation; C Evidence]

Summary Statement 65: Advise patients to stop exercising immediately at the first onset of symptoms, because continued exertion results in worsening of the episode. [Strong Recommendation; D Evidence]

Summary Statement 66: Advise all patients to carry 2 epinephrine auto-injectors and exercise with a partner who can recognize symptoms and administer epinephrine. [Strong Recommendation; D Evidence]

Summary Statement 67: Recognize that medications used prophylactically will not universally prevent symptoms of EIA. [Recommendation; D Evidence]

Exercise-induced anaphylaxis and food-dependent EIA (FDEIA) are uncommon but potentially life-threatening clinical syndromes in which association with exercise is the key defining characteristic.[1] The range of triggering physical activities is broad. EIA is not fully repeatable (ie, the same exercise might not always result in anaphylaxis in a given patient). In FDEIA, the combined ingestion of sensitizing food and exercise is required to induce symptoms. Clinical features and acute management do not differ significantly from other types of anaphylaxis. The pathophysiology of EIA and FDEIA is not fully understood. Different hypotheses concerning the possible influence of exercise on the development of anaphylactic symptoms have been proposed, including increased gastrointestinal permeability,[2,3] blood flow redistribution,[4] and increased osmolality.[5,6] Symptoms of EIA are usually triggered by exercise of moderate intensity, but there is no entirely safe exercise level for patients with EIA.[7] Warm environment, high humidity, and cold environment have been reported to be associated with EIA occurrence in a subset of patients.[8]

Initial symptoms of EIA typically include initially fatigue, diffuse warmth, pruritus, erythema, and urticaria, with progression to angioedema, gastrointestinal symptoms, laryngeal edema, and/or cardiovascular collapse if exercise continues.[7,9] Wheezing can occur, although it is less common than other symptoms, as distinguished from exercise-induced bronchospasm. Some patients experience disabling headache that persists for several days after an episode.[9] Once the patient stops exercising or receives treatment, symptoms can dissipate rapidly or last for several hours. It is not known how often this disorder is fatal, although at least 1 death has been reported.[10]

Many patients require at least 1 other cofactor to be present to develop symptoms with exercise. Reported "co-triggers" include the ingestion of specific foods,[11] the ingestion of any food,[12] NSAIDs,[13,14] alcoholic beverages, menstruation,[8] or seasonal pollen exposure in appropriately sensitized patients.[7] Typically, each trigger is tolerated if there is no association with exercise, that is, patients with food as a co-trigger can eat the food without symptoms or exercise without symptoms, although if they eat the food and then exercise, they will develop anaphylaxis. In general, exposure to the co-trigger occurs first, followed by exercise, with the latter resulting in the onset of symptoms. Ingestion of NSAIDs can precede exercise by up to 24 hours, whereas food or alcohol ingestion typically needs to occur within 4 to 6 hours before exercise. The foods most commonly implicated are wheat, other grains, nuts, and seafood, although many different foods have been reported.[11,12,15] Elimination of these foods might allow the patient to exercise without anaphylaxis,[11,13,16] and similarly these patients often can ingest these foods without anaphylaxis if they do not exercise for 4 to 6 hours after eating them.[11]

The pathophysiology of EIA is not well-understood, although it does appear to be primarily a mast cell–mediated disorder. Skin biopsies have demonstrated degranulation of dermal mast cells after attacks,[17] and transient elevations in plasma histamine[13] and serum tryptase[18] have been documented in case reports. The precise triggers for mast cell activation have not been conclusively identified, and the events during exercise that can alter the activity of mast cells or other leukocytes have not been defined, although the association between ω-5 gliadin and low- and high-molecular-weight glutenin in wheat-induced EIA has been well documented.[19] As mentioned earlier, some theories include issues pertaining to including increased gastrointestinal permeability,[2,3] leading to increased absorption of relevant food allergen, blood flow redistribution[4] (with resultant changes in resident gastrointestinal mast cell populations), and increased osmolality.[5,6] Others have proposed the potential importance of the widespread use of acid-suppressing medications toward an increased risk of developing FDEIA in particular.[20–22]

The diagnosis of EIA can be confirmed by a controlled exercise challenge that demonstrates the elicitation of typical symptoms (eg, treadmill testing); however, it is acknowledged that symptoms can be difficult to reproduce.[23,24] The differential diagnosis includes arrhythmias and other cardiovascular events in addition to vocal cord dysfunction, but such events do not manifest with concomitant pruritus, urticaria, angioedema, or upper airway obstruction. Exercise-induced bronchoconstriction presents with symptoms limited to the airways.

Cholinergic urticaria, a physical urticaria usually limited to the skin, can mimic the early cutaneous symptoms of EIA and is characterized by initially punctate (1–3 mm in diameter) wheals with surrounding erythema of the affected skin.[25] Symptoms are elicited by raising the core body temperature, such as with a hot shower, strong emotion, or spicy food, and can be distinguished by a careful history. A minority of patients with EIA develop punctate urticarial lesions,[26] although most have typical larger wheals (10–15 mm). Exercise is necessary to elicit the symptoms of EIA; passively raising the core body temperature is not sufficient to induce EIA symptoms.[27]

The management of EIA must be individualized, depending on symptom severity, presence of co-triggers, and the patient's desire to continue exercise. Patients must carry 2 epinephrine auto-injectors whenever they exercise. Patients with EIA also should exercise with a partner or in a supervised setting. The companion should be educated with respect to EIA and be capable of administering epinephrine. Patients must be vigilant for early signs or symptoms (eg, flushing or pruritus) and stop exercise immediately if these occur. It is crucial that patients understand the importance of stopping exercise immediately at the first sign of symptoms. For patients with identifiable cofactors, avoidance of these triggers could allow them to resume exercise safely.[28]

Some pharmacologic protection seems possible but preventative regimens are not universally effective. One report described the protective effect of cetirizine and montelukast in a patient with FDEIA,[29] and evidence exists that pretreatment with mast cell stabilizers can have a preventive effect in FDEIA.[30,31] Similar effects

have been observed after pretreatment with ketotifen.[32,33] Many experts also have observed anecdotal benefit from the use of ketotifen in such patients, but it is important to recognize that there is no good evidence for any of these preventive regimens in EIA.

Fortunately, many patients with EIA report fewer attacks over time, but much of this improvement could be attributable to modifications in exercise habits and/or self-recognition of co-triggers. A questionnaire administered to 279 patients with EIA persisting for longer than 10 years found that the average number of episodes per year decreased from 14.5 at the time of diagnosis to 8.3 in the year of the study.[7] Patients reported avoiding exercise during extremely hot, cold, or humid weather conditions, during pollen season (pollen-allergic patients), after eating, and after taking NSAIDs.[9] Thus, with proper counseling and careful self-monitoring, most patients can continue exercise and develop fewer attacks over time.

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IX. Anaphylaxis to Subcutaneous AIT Extract (vaccine)

Summary Statement 68: Before initiating subcutaneous AIT injections, inform patients about the risk of immediate and late-onset (beginning after 30 minutes) systemic allergic reactions and the minimal risk of life-threatening and fatal anaphylaxis. [Recommendation; C Evidence]

Summary Statement 69: Administer allergen injections in a supervised clinic setting staffed by personnel trained in recognition and treatment of anaphylaxis and observe patients for at least 30 minutes after injections. [Recommendation; C Evidence]

Summary Statement 70: Because most fatal anaphylactic reactions to allergen injections have been reported in patients with uncontrolled asthma, assess current asthma control at each visit before administration of allergen injection(s) in patients with asthma receiving immunotherapy. [Recommendation; C Evidence]

Summary Statement 71: Consider alternatives to ACE inhibitors and β-blockers as possible antihypertensive therapy in the setting of immunotherapy for venom anaphylaxis. [Recommendation; C Evidence]

Summary Statement 72: Start or continue patient AIT in patients who take β-blockers only if the benefits in such patients clearly outweigh the risks (eg, patients with stinging insect hypersensitivity). [Recommendation; C Evidence]

Summary Statement 73: Recognize the potential possible risk factors that can contribute to severe anaphylaxis from immunotherapy injections and implement measures to prevent and manage severe systemic allergic reactions. [Recommendation; C Evidence]

In an annual survey of AIT SRs conducted in North America, practicing allergists reported 1 SR in every 1,000 injection visits (0.01%).[1–3] Nearly all (97%) reported SRs associated with SCIT were considered mild or moderate in severity and only 3% to 4% of reported reactions were consistent with severe anaphylaxis (ie, severe airway compromise and/or hypotension).[3] In a retrospective survey of allergists in North America, near-fatal life-threatening anaphylaxis was estimated to occur in every 1 million injections (0.0001%).[4] In retrospective surveys of AIT fatalities conducted before 2001, fatal anaphylactic reactions were estimated at 1 event in every 2 to 2.5 million injections, or 3 fatal events annually.[5,6] In a North American surveillance study of SRs, practicing allergists reported that 14% of all SRs started 30 minutes after injections.[2]

Allergen injections should be administered only in health care facilities with proper equipment for the treatment of anaphylaxis (see Section II, Office Management of Anaphylaxis and the tables

therein), including at least epinephrine, oxygen, oral airway, and equipment for the administration of intravenous fluids and medications. Injections should be administered in a setting where policies are in place to minimize risk of anaphylaxis, including standard operating procedures designed to lower the risk of dosing errors and ensure proper training of personnel in the treatment of anaphylaxis.[7] Because home administration has been associated with suboptimal treatment of injection-related anaphylaxis and fatal reactions, AIT injections should not be administered at home, except in rare situations in which the benefits of home administration clearly outweigh risks, such as patients with potentially life-threatening reactions to stinging insects who are at increased risk of insect stings, and only after informed consent has been obtained.[8,9]

Most fatal reactions have begun within 30 minutes after AIT injections.[5,6,10] In a North American retrospective 12-year survey of life-threatening SRs, 4% of life-threatening nonfatal reactions began after 30 minutes and fatal reactions in 3 of 17 patients (18%) started more than 30 minutes after injection.[4,5] Based on a recently published surveillance study of SRs, late reactions beginning 30 minutes after injections represented 14% of all reported SCIT-related SRs; of these, only 3% were considered severe anaphylactic reactions (ie, involving severe airway compromise and/or hypotension) and all patients were successfully resuscitated.[2] Based on these findings, it is recommended that patients remain and be observed for at least 30 minutes after an allergen injection(s) in a supervised medical outpatient facility staffed with medical personnel trained to recognize and treat anaphylactic reactions, including timely administration of epinephrine.[7] For patients experiencing late-onset reactions, the postinjection observation period for subsequent AIT injections should be appropriately extended beyond 30 minutes.[7]

Poor asthma control is considered a major contributing factor to fatal reactions after AIT injections. A large proportion of patients who had fatal anaphylactic reactions after AIT injections had histories of poorly controlled asthma, decreased lung function, and asthma exacerbations.[5,6,10] Most of these patients had a history of emergency department visits and hospitalizations for treatment of acute asthma.[5] Therefore, asthma control should be assessed in all patients with asthma before administering allergen injections by evaluating for a recent increase in asthma symptoms with or without measurement of lung function (eg, peak expiratory flow) to detect recent decrements in lung function. Prescreening can be particularly important for that subset of patients with asthma who poorly perceive their level of control. Asthma must be controlled before AIT injections are given.[7] Annual reports of AIT injection-related fatal reactions have markedly decreased since 2008, perhaps attributable to widespread preinjection asthma screening by practicing allergists.[3]

Concomitant treatment with ACE inhibitors does not appear to increase the overall incidence of SRs to venom or aeroallergen AIT injections.[11,12] There are 3 anecdotal reports of severe anaphylaxis with hymenoptera venom injections. In all cases, patients undergoing treatment for allergy to insect stings experienced anaphylaxis with severe hypotension within minutes after administration of a subcutaneous injection of hymenoptera venom and were successfully resuscitated. In all cases, hymenoptera build-up and maintenance venom doses could be safely administered without reactions after ACE inhibitors were withheld for at least 24 hours before injections.[13,14] There also are anecdotal reports of fatal anaphylactic reactions after aeroallergen injections occurring in patients receiving ACE inhibitors.[5] There is insufficient evidence to indicate that withholding ACE inhibitors prevents severe anaphylaxis after aeroallergen injections. Thus, based on current evidence, physicians should consider withholding ACE inhibitors for at least 24 hours before administering build-up and maintenance venom injections to prevent possible severe SRs.

There are anecdotal reports of fatal reactions to SCIT in patients receiving β-blockers.[8,9,15] However, prospective and retrospective studies have indicated that concomitant treatment with β-adrenergic blocking agents does not increase the likelihood of SRs in patients receiving AIT injections with aeroallergens or venoms.[11,16,17] Beta-adrenergic blocker treatment can be a contributing risk factor for anaphylaxis from causes other than AIT and increase the need for subsequent treatment in the hospital.[18,19] Therefore, a cautious attitude should be adopted toward the concomitant use of β-adrenergic blockers and SCIT. Immunotherapy is relatively contraindicated in patients with asthma receiving β-blockers.[20] Benefits of AIT with hymenoptera venoms clearly outweigh risks associated with β-blockers, such as potential ineffectiveness of epinephrine in patients on β-blockers, patients with confirmed anaphylaxis to stinging insects, and patients with cardiovascular disease requiring uninterrupted treatment with β-blockers. Such patients tolerate VIT with no greater frequency or severity of SRs than similar patients not receiving β-blockers.[17]

A history of SRs to AIT injections has been reported in most patients with fatal anaphylactic reactions to SCIT.[8,9] In patients with prior severe SRs, physicians should consider management options including adjustment of allergen doses of future AIT injections or, if risk exceeds potential benefit, discontinuation of AIT injections. Surveys of fatal anaphylactic reactions to AIT have indicated that epinephrine treatment was delayed or not given in 43% of reported events.[8,9] Thus, medical personnel administering injections should be prepared and trained to administer adequate doses of intramuscular epinephrine within minutes after recognition of anaphylaxis. Dosing errors are common and have been implicated in one third of fatal reactions and 25% of near-fatal reactions.[4–6,21] Standard procedures should be implemented to decrease dosing errors, including use of patient-specific vials, standard dosage sheets, and double checking of patient identity to ensure the correct patient is receiving the correct injection.[7,21] Nearly half of fatal and near-fatal anaphylactic reactions to AIT injections occurred during peak allergy seasons.[5,6] A recent surveillance study of practicing allergists in North American found that practices that always decrease maintenance allergen doses during peak pollen season were less likely to encounter moderate and severe allergic SRs to AIT injections. Based on this retrospective evidence, physicians should consider adjusting AIT doses during peak pollen seasons in all or selected patients receiving pollen allergens.

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X. Anaphylaxis in Mastocytosis, MMAS, and MCAS

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Summary Statement 74: Recognize that patients with SM or MMAS are at increased risk for anaphylaxis. [Strong Recommendation; B Evidence]

Summary Statement 75: Obtain a bone marrow biopsy specimen from patients fulfilling the criteria for possible mast cell disease and perform immunohistochemical staining with antibody directed to mast cell tryptase, recognizing that demonstration of coexpressed CD2 and CD25 in CD117 (KIT)-positive mast cells by flow cytometry of bone marrow aspirates or immunohistochemical analysis of bone marrow biopsy specimens provides the most sensitive and specific support for the diagnosis of SM. [Recommendation; B Evidence]

Summary Statement 76: Treat anaphylaxis in a patient with SM, MMAS, or MCAS in the same manner as anaphylaxis in a patient experiencing an SR to a known allergenic substance. [Strong Recommendation; D Evidence]

Summary Statement 77: Evaluate a patient with idiopathic anaphylaxis or insect sting-induced anaphylaxis for SM if the patient has cutaneous mastocytosis, unexplained organomegaly, an unexplained cytopenia or thrombocytopenia, recurrent severe episodes of anaphylaxis, or an elevated serum tryptase level obtained during a period when no SR is recognized. [Strong Recommendation; D Evidence]

Summary Statement 78: Provide patients with SM, MMAS, and MCAS with AIE to use in the event of anaphylaxis. [Strong Recommendation; D Evidence]

Spontaneous or provoked episodes of anaphylaxis can occur in patients diagnosed with mastocytosis or MMAS. The cumulative incidence of anaphylaxis in adult patients with SM has been reported to be as high as 49%.[1] Patients with SM or MMAS also have been identified within groups of patients with anaphylaxis to stinging insects or anaphylaxis without an identifiable cause in whom the diagnosis of SM had not been previously made because the patients lacked obvious features of mastocytosis such as mastocytosis-associated skin lesions.[2,3] Idiopathic anaphylaxis also can occur in patients who meet the suggested criteria for MCAS, a disease of exclusion in which there is no identifiable cause for mediator release but the patient meets the pathologic criteria for mast cell activation. The challenge is to recognize SM and when to suspect SM or MMAS if the patient experiences unexplained episodes of anaphylaxis. Episodes of anaphylaxis in patients with SM, MMAS, or MCAS are managed in the same way as when anaphylaxis follows exposure to an allergen known to provoke allergic SRs.

Systemic mastocytosis is characterized by the abnormal growth and accumulation of mast cells in at least 1 organ. SM can present with or without skin lesions and might show an indolent or aggressive clinical course, in some cases complicated by concomitant emergence of a clonal non-mast cell lineage disorder. This has led to further classification of mastocytosis based on hematologic findings, molecular markers, tryptase level, and cluster differentiation markers such as CD25, thereby grouping patients into better-defined clinical categories, which have been adopted by the WHO (Table X-1).[4] The diagnosis of SM requires that 1 major criterion and 1 minor criterion or 3 minor criteria be present. The WHO criteria for variants of SM are presented in Table X-2. The prognosis of patients with adult mastocytosis is dependent on the extent of disease and presence of an associated hematologic disorder. Patients with indolent SM tend to remain within this category of disease, although a subset will progress to a more aggressive form of disease. For children with isolated urticaria pigmentosa (UP), at least 50% of cases are reported to resolve by adulthood.[5] Patients with SM with an associated non-mast cell lineage clonal hematologic disorder have a course that depends largely on the prognosis of the specific hematologic disorder.[6]

Systemic effects of mast cell disease result from the release of mast cell mediators into the circulation and include anaphylaxis, flushing, pruritus, hypotension, syncope, palpitations, and tachycardia. Gastrointestinal symptoms include nausea, vomiting, abdominal cramping, bloating, and/or diarrhea. For some patients, the most bothersome complaints include fatigue, weakness, anorexia, weight loss, low-grade fevers, night sweats, musculoskeletal pain, headaches, depression, altered attention span, irritability, and even subtle cognitive deficits. Attacks in some individuals are precipitated by heat, cold, pressure, alcohol, medications (eg, opiates, NSAIDs, and estrogens), RCM, and venoms. Local sequelae of mastocytosis are due largely to the effects of mast cell collections at specific organ sites and include fibrosis and osteoporosis.[7–12]

Indolent SM is the most common form of SM in adults. It often presents with UP and further evaluation will disclose mast cell involvement at various organ sites. Significant organ dysfunction is usually absent, and the prognosis is generally good. The vast majority of adult patients with indolent SM demonstrate bone marrow mast cell infiltration[4,13] consisting of focal aggregates of mast cells.[4] Clonal mast cells generally express CD2 and/or CD25 and the D816V mutation.[4,14] Other forms of SM are less common and are listed in Table X-1.

The diagnosis of mastocytosis is based on the finding of confluent clusters of mast cells in affected organ sites or diffuse infiltration with replacement of normal tissue by mast cells coupled with clinical signs and symptoms and laboratory test results that are consistent with mast cell disease.[4,6] Examination of the bone marrow includes an inspection of the bone marrow biopsy specimen and the aspirate. Immunohistochemical staining with antibody directed to mast cell tryptase is the method of choice to visualize mast cells.[4,15–18] In most patients with SM, tryptase-positive infiltrates are composed of spindle-shaped mast cells. The coexpression of CD2 and/or CD25 in CD117 (KIT)-positive mast cells by flow cytometry of bone marrow aspirates or by immunohistochemical analysis of bone marrow biopsy specimens appears to be the most sensitive and specific method to support the diagnosis of SM in bone marrow.[11,19,20]

Serum mast cell tryptase is the most commonly used surrogate marker for SM and is quantified using a commercial enzyme-linked immunosorbent assay.[21,22] A total tryptase level higher than 20 ng/

Table X-1
World Health Organization diagnostic criteria for cutaneous and systemic mastocytosis

Cutaneous mastocytosis	Typical clinical findings of urticaria pigmentosa or maculopapular cutaneous mastocytosis, diffuse cutaneous mastocytosis, or solitary mastocytoma and typical infiltrates of mast cells in a multifocal or diffuse pattern at skin biopsy examination
Systemic mastocytosis	Diagnosis of systemic mastocytosis is made if 1 major criterion and 1 minor criterion are present or if 3 minor criteria are met
Major criterion	Multifocal, dense infiltrates of mast cells (≥15 in aggregates) detected in sections of bone marrow and/or another extracutaneous organ and confirmed by tryptase immunohistochemistry or other special stains
Minor criteria	
A	In biopsy sections of bone marrow or other extracutaneous organs, >25% of mast cells in the infiltrate are spindle-shaped or have atypical morphology; or, of all mast cells in bone marrow aspirates smears, >25% are immature or atypical mast cells
B	Detection of activating point mutation at codon 816 of KIT in bone marrow, blood, or another extracutaneous organ
C	Mast cells in bone marrow, blood, or another extracutaneous organ express CD117 with CD2 and/or CD25
D	Serum total tryptase persistently >20 ng/mL in the absence of associated clonal myeloid disorder

mL is suggestive of mastocytosis and has been included as a minor criterion in the diagnosis of SM.[4,11] Normal baseline levels in healthy individuals are generally no higher than 12 ng/mL. Tryptase levels no higher than 20 ng/mL have been detected in patients with cutaneous mastocytosis and in those with limited systemic disease.[23]

Various metabolites of arachidonic acid also are elevated in patients with mastocytosis. These include urinary prostaglandin D_2 or 9α,11β-dihydroxy-15-oxo-2,2,18,19-tetranorprost-5-ene-1,20-dioxic acid, and plasma thromboxane B_2 and its metabolites. Because the source of prostaglandins and thromboxanes in mastocytosis is not exclusively limited to mast cells, reliance on assays that measure these metabolites is unlikely to be sufficiently specific for diagnostic purposes. If measured, then elevations in at least 1 mast cell mediator, such as 24-hour urine level for histamine metabolites, raise the suspicion of mastocytosis and warrant further diagnostic evaluation.

Identification of genetic markers of mastocytosis, such as point mutations in c-kit, help support the diagnosis of mastocytosis. The identification of the D816V mutation fulfills a minor diagnostic criterion in the diagnosis of mastocytosis. Analysis for c-kit mutations is best performed on bone marrow and, specifically, on sorted malignant mast cells to increase sensitivity. In patients with coexisting eosinophilia, peripheral blood should be examined for the presence of the FIP1L1/PDGFRα fusion gene.[10]

An important component of management of all categories of mastocytosis is patient avoidance of triggering factors such as alcohol and NSAIDs in sensitive patients (pressure, friction, or extremes of temperature) and agents to which the patient is specifically allergic.[3,5,24] As with other syndromes in which patients might be at risk for severe type I hypersensitivity reactions, patients with mastocytosis should carry AIE and be skilled in self-administration. *Monoclonal mast cell activating syndrome* is a term adopted by a consensus conference to be applied to patients who are found to have 1 or 2 minor diagnostic criteria for mastocytosis but lack the full diagnostic criteria for systemic disease.[11] Patients with such findings have been identified within groups of patients diagnosed with idiopathic anaphylaxis and patients with anaphylaxis to stinging insects.[2,3,25–44] Most of these patients have a tryptase level below 20 ng/mL. The suggestion has been made that these studies might be identifying patients with an advancing clonal mast cell disorder that one day might meet the diagnostic

Table X-2
World Health Organization criteria for variants of systemic mastocytosis

Indolent systemic mastocytosis (ISM)*	Meets criteria for SM. No "C" findings (see below). No evidence of AHNMD. In this variant, the mast cell burden is low and skin lesions are usually present.
Bone marrow mastocytosis	As above for ISM, with bone marrow involvement but no skin lesions.
Smoldering systemic mastocytosis*	As above for ISM, but with ≥2 "B" findings and no "C" findings.
Systemic mastocytosis with associated clonal, hematologic non-mast cell lineage disease (SM-AHNMD)	Meets criteria for SM and criteria for AHNMD (myelodysplastic syndrome, myeloproliferative neoplasms, acute myeloid leukemia, lymphoma, or other hematologic neoplasm that meets the criteria for distinct entity in World Health Organization classification).
Aggressive systemic mastocytosis	Meets criteria for SM with ≥1 "C" finding. No evidence of mast cell leukemia. Usually without skin lesions.
Lymphadenopathic mastocytosis with eosinophilia	Progressive lymphadenopathy with peripheral blood eosinophilia, often with extensive bone involvement, and hepatosplenomegaly but usually without skin lesions. Cases with rearrangement of PDGFRA are excluded.
Mast cell leukemia	Meets criteria for SM. Bone marrow biopsy examination shows diffuse infiltration by atypical, immature mast cells. Bone marrow aspirate smears show ≥20% mast cells. Mast cells account for ≥10% of peripheral blood white cells. Variant: leukemic mast cell leukemia as above, but <10% of white blood cells are mast cells. Usually without skin lesions.
Mast cell sarcoma	Unifocal mast cell tumor. No evidence of SM. Destructive growth pattern. High-grade cytology.
Extracutaneous mastocytoma	Unifocal mast cell tumor. No evidence of SM. No skin lesions. Nondestructive growth pattern. Low-grade cytology
"B" findings	
1	Bone marrow biopsy showing >30% infiltration by mast cells (focal, dense aggregates) and/or serum total tryptase level >200 ng/mL.
2	Signs of dysplasia or myeloproliferation in non-mast cell lineages, but insufficient criteria for definitive diagnosis of a hematopoietic neoplasm with normal or slightly abnormal blood cell counts.
3	Hepatomegaly without impairment of liver function, and/or palpable splenomegaly without hypersplenism, and/or lymphadenopathy.
"C" findings	
1	Bone marrow dysfunction manifested by ≥1 cytopenia (absolute neutrophil count $<1.0 \times 10^9$/L, hemoglobin <10 g/dL, or platelet count $<100 \times 10^9$/L), but no obvious non-mast cell hematopoietic malignancy.
2	Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension.
3	Skeletal involvement with large osteolytic lesions and/or pathological fractures.
4	Palpable splenomegaly with hypersplenism.
5	Malabsorption with weight loss owing to gastrointestinal mast cell infiltrates.

criteria for SM, although this is a controversial area requiring an understanding of both sides of the issue.

Currently, such patients are treated under guidelines for the treatment of anaphylaxis. Follow-up at yearly intervals is recommended. The follow-up examination should include a physical examination to rule out evolving organomegaly or lymphadenopathy, a serum tryptase level to determine whether there is indirect evidence of an expanding mast cell compartment, and a complete blood cell count with differential and platelet counts to help rule out an evolving hematologic disorder.

The term *mast cell activation syndrome* is applied as a diagnosis for individuals who present with episodic allergic-like signs and symptoms such as anaphylaxis flushing, urticaria, diarrhea and wheezing involving at least 2 organ systems and in which an extensive medical evaluation has failed to identify an etiology. The assumption is that individuals to whom this diagnosis is applied are having episodes owing to a release of mediators associated with hyperreactivity of mast cells that then activate spontaneously. Diagnostic criteria have been proposed to separate this possibility from other causes of such clinical findings. These additional criteria include response to anti-mediator therapy and an elevation in a validated urinary or serum marker of mast cell activation such as serum tryptase with an episode.[45,46] See earlier sections describing bone marrow biopsy findings in patients with mast cell disease. Once the diagnostic criteria are met, therapy is symptomatic. Anaphylaxis is treated using the same management strategies used to treat patients with anaphylaxis to identifiable allergens.

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XI. Unusual Presentations of Anaphylaxis

Summary Statement 79: Be aware that anaphylaxis can present with unusual clinical manifestations such as chest pain and that these patients might require treatment with epinephrine. [Recommend; C Evidence]

In a recent survey of paramedics,[1] 99% could recognize a classic case of anaphylaxis but only 3% recognized an atypical case. Only 46% identified epinephrine as the initial drug of choice. Such data raise concern that there is a link between unrecognized anaphylaxis and underuse of epinephrine,[2,3] as indicated by management of patients with anaphylaxis in the emergency department.[4–9] Therefore, better recognition of atypical or unusual presentations of anaphylaxis should intuitively lead to greater use of epinephrine and perhaps even a decrease in anaphylactic morbidity and mortality.

In 2004, a select international group of experts on anaphylaxis met at the National Institutes of Health to establish criteria for defining anaphylaxis.[10] Their conclusions were subsequently published as the NIAID/Anaphylaxis Network Definition of Anaphylaxis.[11] They concluded that there were 3 presentations consistent with anaphylaxis: (1) an acute onset of a reaction that included the skin (mucosal tissue) and involvement of the respiratory tract and/or a decrease in blood pressure; (2) the rapid onset of a reaction after exposure to a likely allergen that involved 2 organ systems (respiratory tract, skin, decrease in blood pressure, and/or persistent gastrointestinal symptoms); or (3) a decrease in blood pressure alone after exposure to a known allergen. However, they also stated that "There without doubt will be patients who present with symptoms not yet fulfilling the criteria for anaphylaxis yet in whom it would be appropriate to initiate therapy with epinephrine." In 2012, a study was performed to validate the definitions proposed at the NIAID meeting.[12] The sensitivity of these definitions was 97%, the specificity was 83%, the negative predictive value was 98%, the positive predictive value was 69%, the positive likelihood ratio was 5.48, and the negative likelihood ratio was 0.04.

Despite the apparent success of these definitions of anaphylaxis, identification of patients who present with atypical anaphylaxis remains a problem based on published emergency department data. In one study, only 43% of patients in anaphylaxis were diagnosed as having anaphylaxis.[13] In another study, 75% of anaphylactic reactions were not coded as anaphylaxis.[14] The underuse of epinephrine in the treatment of anaphylaxis is to some degree understandable if the correct diagnosis is not made.

What should be considered an atypical presentation of anaphylaxis? Patients in anaphylaxis can develop cardiac manifestations (1) secondary to respiratory compromise or hypotension, (2) as a direct effect of treatment with epinephrine or vasopressors, and/or (3) owing to vasoactive mediator release from mast cells in the heart. It is not always recognized that there are abundant mast cells in the human heart that are located in strategic areas (eg, adventitia of large coronary arteries), are functional (secrete large amounts of vasoactive mediators), and have been associated with a negative inotropic effect, myocardial depression, and arteriolar vasoconstriction.[15–19] Ominously, the number and density of cardiac mast cells are increased in patients with ischemic heart disease and dilated cardiomyopathies.[19] Therefore, it should not be surprising that anaphylaxis can present with prominent cardiac symptoms, such as chest pain in children[14] and adults,[21] electrocardiographic changes,[21,22] and even myocardial damage.[23,24] As a further indication of the role that mast cells might play in acute cardiac events, they have been identified in atherosclerotic lesions with evidence that they contribute to the atherogenesis of these lesions.[25] Stress through the release of corticotropin-releasing hormone also has been shown to relate directly to coronary artery disease through activation of coronary mast cells.[26]

Anaphylaxis also can present as abdominal manifestations, with and without gastrointestinal symptoms,[27] and can be misdiagnosed as abdominal trauma.[28]

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