


The diagnosis and management of anaphylaxis practice parameter: 2010 Update

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Key words: Anaphylaxis, drug allergy, latex allergy, food allergy, exercise anaphylaxis, intraoperative anaphylaxis

To read the Practice Parameter in its entirety, please download the online version of this article from www.jacionline.org. The full document follows the Executive Summary.

EXECUTIVE SUMMARY

Evaluation and management of the patient with a history of episodes of anaphylaxis

The history is the most important tool to determine whether a patient has had anaphylaxis and the cause of the episode (C). A thorough differential diagnosis should be considered, and other conditions should be ruled out (C). Laboratory tests can be helpful to confirm a diagnosis of anaphylaxis or rule out other causes. Proper timing of such tests (eg, serum tryptase) is essential (B). In the management of a patient with a previous episode of anaphylaxis, education is necessary. Emphasis on early treatment, specifically the self-administration of epinephrine, is essential

Abbreviation used

NLR: Natural rubber latex

(C). The patient can be instructed to wear and/or carry identification denoting the condition (eg, MedicAlert bracelet; MedicAlert Foundation of the United States, Turlock, Calif) and can also be instructed to have telephone numbers for paramedic rescue squads and ambulance services on hand. A written action plan can be helpful in this regard (C).

Office management of anaphylaxis

Anaphylaxis is an acute, life-threatening systemic reaction with varied mechanisms, clinical presentations, and severity that results from the sudden systemic release of mediators from mast cells and basophils. (B) The more rapidly anaphylaxis develops, the more likely the reaction is to be severe and potentially life-threatening. (C) Prompt recognition of signs and symptoms of anaphylaxis is crucial. If there is any doubt, it is generally better to administer epinephrine. (C) Epinephrine and oxygen are the most important therapeutic agents administered in anaphylaxis. Epinephrine is the drug of choice, and the appropriate dose should be administered promptly at the onset of apparent anaphylaxis. (C) Appropriate volume replacement either with colloid or crystalloids and rapid transport to the hospital are essential for patients who are unstable or refractory to initial therapy for anaphylaxis in the office setting. (B) Medical facilities should have an established plan of action to deal with anaphylaxis that is regularly practiced and the appropriate equipment to treat anaphylaxis. (B) Physicians and office staff should maintain clinical proficiency in anaphylaxis management. (D) In addition, telephone numbers for paramedical rescue squads and ambulance services might be helpful to have on hand. (C)

SPECIFIC TRIGGERS/SETTING FOR ANAPHYLAXIS

Anaphylaxis to foods

Food is the most common cause of anaphylaxis in the outpatient setting, and food allergens account for 30% of fatal cases of anaphylaxis. (D) The most commonly implicated foods responsible for food-induced anaphylaxis include peanuts, tree nuts, fish, shellfish, cow's milk, soy, and egg. In addition, sesame seed has recently been identified as a significant cause of food-induced anaphylaxis. (C) Common themes associated with fatal food anaphylaxis include the following: reactions commonly involve peanuts and tree nuts; cutaneous and respiratory symptoms are frequently observed; victims are typically teenagers and young adults; patients have a previous history of food allergy and asthma; and there is a failure to administer epinephrine promptly. (C) As is the case of anaphylaxis following other agents, asthma is a risk factor for more severe food-induced anaphylaxis. (C) Biphasic anaphylactic reactions can occur in up to 25% of fatal and near-fatal food reactions. (C) Serum tryptase measurements may not be elevated in cases of food-induced anaphylaxis. (C) The rapid use of injectable epinephrine has been shown to be effective in the initial management of food-induced anaphylaxis, but subsequent doses may be needed. (C) Patients who experience anaphylaxis should be observed for longer periods if they have experienced food-induced anaphylaxis. (C) Food-dependent, exercise-induced anaphylaxis is a unique clinical syndrome in which anaphylaxis occurs within a few hours of specific

food ingestion or any meal, and exercise. (C) Patients with food allergy should pay close attention to food advisory labeling (eg, "may contain"), which has become more prevalent. (C)

Natural rubber latex-induced anaphylaxis

There are 3 groups at high risk of reaction to latex: health care workers, children with spina bifida and genitourinary abnormalities, and workers with occupational exposure to latex. (C) *In vitro* assays for IgE to natural rubber latex (NRL) are typically recommended as a first step in evaluating latex sensitivity. However, because of their suboptimal diagnostic predictive value, positive and negative results must be interpreted on the basis of the history. If the test is positive with a high clinical likelihood, latex sensitivity would be reasonable to pursue. In contrast, if the test is negative with a high clinical likelihood, latex sensitivity still must be considered. (C) A standardized commercial skin test reagent for NRL is not available in the United States. Allergists have prepared NRL extracts from gloves to use for clinical testing. It should be noted, however, that such extracts prepared from gloves demonstrate tremendous variability in the content of NRL allergen. Nevertheless, skin prick tests with NRL extract to identify IgE-mediated sensitivity should be considered if patients are members of high-risk groups or have a clinical likelihood of NRL allergy and have negative *in vitro* tests. (C) Patients with spina bifida (regardless of a history of NRL allergy) and patients with a positive history of NRL allergy ideally should have all medical-surgical-dental procedures performed in a NRL-safe environment. (D) A NRL-safe environment is an environment in which no NRL gloves are used in the room or surgical suite and there are limited NRL accessories (catheters, adhesives, tourniquets, and anesthesia equipment or devices) that come in contact with the patient. (D) In health care settings, general use of NRL gloves with negligible allergen content, powder-free NRL gloves, and nonlatex gloves and medical articles should be considered in an effort to minimize patient exposure to latex. Such an approach can minimize NRL sensitization of health care workers and patients and reduce the risk of reactions to NRL in previously sensitized individuals. (D) Patients with a diagnosis of NRL allergy by history and/or skin testing can wear a medical identification bracelet, carry a medical identification card, or both. If patients have a history of anaphylaxis to NRL, it is important for them to carry autoinjectable epinephrine. (D)

Anaphylaxis during general anesthesia, the intraoperative period, and the postoperative period

The incidence of anaphylaxis during anesthesia has been reported to range from 1 in 4000 to 1 in 25,000. Anaphylaxis during anesthesia can present as cardiovascular collapse, airway obstruction, and/or skin manifestation. (C) It can be difficult to differentiate between immune and nonimmune mast cell-mediated reactions and pharmacologic effects from the variety of medications administered during general anesthesia. In addition, cutaneous manifestations of anaphylaxis are less likely to be apparent when anaphylaxis occurs in this setting. (B) The evaluation of IgE-mediated reactions to medications used during anesthesia can include skin testing to a variety of anesthetic agents. (B) Specifically, thiopental allergy has been documented by skin tests. (B) Neuromuscular blocking agents such as succinylcholine can cause nonimmunologic histamine release, but there have also been reports of IgE-mediated reactions in some patients. (B) Reactions to opioid analgesics are usually caused by direct mast cell mediator release rather than IgE-

dependent mechanisms. (B) Antibiotics that are administered perioperatively can cause immunologic or nonimmunologic reactions. (B) Protamine can cause severe systemic reactions through IgE-mediated or nonimmunologic mechanisms. (B) Blood transfusions can elicit a variety of systemic reactions, some of which might be IgE-mediated or mediated through other immunologic mechanisms. (B) Methylmethacrylate (bone cement) has been associated with hypotension and various systemic reactions, although no IgE mechanism has been documented. (C) The management of anaphylactic reactions that occur during general anesthesia is similar to the management of anaphylaxis in other situations. (B)

Seminal fluid-induced anaphylaxis

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. (C) Postcoital local reactions to human seminal plasma are probably IgE-mediated on the basis of the successful response to rapid seminal plasma desensitization. (C) A history of atopic disease is the most consistent risk factor for seminal fluid-induced anaphylaxis. (C) The diagnosis of seminal plasma anaphylaxis may 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 via seminal plasma. (D) Greater than 90% of the allergenic proteins range between 12 and 75 kd. Prostate-specific antigen has been demonstrated to be a relevant allergen in some cases. (C) 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. (C) Subcutaneous immunotherapy to properly prepared fractions of seminal plasma collected from male partners has been successful in preventing anaphylaxis to seminal plasma. (C) Successful intravaginal graded challenge with whole seminal plasma of the male partner has been reported in a few cases, but the duration of protection is unknown. This treatment approach is advocated before pursuing desensitization using relevant seminal plasma protein fractions. (C) Patients with seminal plasma allergy may be able to conceive without undergoing desensitization, by artificial insemination with washed spermatozoa. (C)

Exercise-induced anaphylaxis

Exercise-induced anaphylaxis is a heterogeneous form of anaphylaxis in which exercise is the immediate trigger for the development of symptoms. Typical symptoms include extreme fatigue, warmth, flushing, pruritus, and urticaria, occasionally progressing to angioedema, wheezing, upper airway obstruction, and collapse. (A) The pathophysiologic events during exercise that precipitate symptoms are not known, although promising lines of research exist. (C) Some patients experience symptoms only if other contributing factors or cotriggers are present in association with exercise. These cotriggers include ingestion of specific foods—or in some patients, ingestion of any food—nonsteroidal anti-inflammatory drugs, and high pollen levels. (C) The clinical history should focus on identification of these possible cotriggers. Evaluation for sensitization to food allergens, particularly grains and seafood, can be performed. The diagnosis is usually made on the basis of the history and exclusion of other disorders. Exercise challenge testing does not consistently

reproduce symptoms. (C) All patients with exercise-induced anaphylaxis must be advised to stop exercising immediately at the first sign of symptoms because continued exertion causes the attacks to worsen. In addition, all patients should carry epinephrine autoinjectors and exercise with a partner who can recognize symptoms and administer epinephrine if necessary. (D) Prophylactic medications are not effective for preventing attacks in the majority of patients, although a small subset does appear to benefit from daily administration of H1 antihistamines. (D) The prognosis of patients with exercise-induced anaphylaxis is generally favorable, although at least 1 fatality has been reported. Most patients experience fewer and less severe attacks over time. It is unclear whether this is the result of trigger avoidance or a change in the underlying condition. (C)

Idiopathic anaphylaxis

The symptoms of idiopathic anaphylaxis are identical to those of episodes related to known causes. (C) Patients with idiopathic anaphylaxis should receive an intensive evaluation, including a meticulous history to rule out a definite cause of the events. (C) There might be a need for specific laboratory studies to exclude systemic disorders such as indolent systemic mastocytosis. This might include a measurement of serum tryptase when the patient is asymptomatic, measurement of total tryptase during or within 4 hours of an acute episode, and the ratio of mature (β) tryptase to total tryptase during an episode. To exclude hereditary angioedema or acquired C1 inhibitor deficiency, a C4 concentration can be obtained because it will be reduced during or in the absence of severe angioedema in those conditions but normal in idiopathic anaphylaxis. (C) There might be a need for selective skin testing for detection of anti-food IgE antibodies when foods have been ingested within 2 hours of the onset of an episode. (C) Empiric use of oral corticosteroids combined with H1 antagonists has been demonstrated to reduce the frequency/severity of episodes. (C) Patients with idiopathic anaphylaxis should carry epinephrine, should know the indications for self-administration, and can carry information denoting their condition. (C)

Anaphylaxis and allergen immunotherapy

There is a small risk of near-fatal and fatal anaphylactic reactions to allergen immunotherapy. (C) Patients with asthma, particularly if poorly controlled, are at higher risk for serious potentially life-threatening anaphylaxis to allergen immunotherapy injections. (C) There is concern that patients taking β -adrenergic blocking agents may be at an increased risk of having a systemic reaction to allergen immunotherapy injections that is difficult to treat. (B) Allergen immunotherapy vaccines should be administered only by health care professionals trained in the recognition and treatment of anaphylaxis, only in health care facilities with the proper equipment for the treatment of anaphylaxis, and in clinics with policies and procedures that minimize the risk of anaphylaxis. (D)

Anaphylaxis to drugs and biological modifiers

Low-molecular-weight medications induce an IgE-mediated reaction only after combining with a carrier protein to produce a complete multivalent antigen. (B) Penicillin is the most common cause of drug-induced anaphylaxis. (C) Penicillin spontaneously degrades to major and minor antigenic determinants, both of which should be included in skin testing for penicillin hypersensitivity. (B) The negative predictive value of penicillin skin testing

with both major and minor determinants (for immediate-type reactions) is between 97% and 99% (depending on the reagents used), and the positive predictive value is at least 50%. (B) The extent of allergic cross-reactivity between penicillin and cephalosporins is unknown but appears to be low. Four percent of patients proven to have penicillin allergy by means of penicillin skin testing react to cephalosporin challenges. (C) Patients with a history of penicillin allergy who have negative penicillin skin test responses can safely receive cephalosporins. (B) Patients who need to receive a cephalosporin and who have a history of penicillin allergy and a positive penicillin skin test response can (1) receive an alternate (non- β -lactam) antibiotic, (2) receive a cephalosporin through graded challenge, or (3) receive a cephalosporin through rapid desensitization. (C) Aztreonam does not cross-react with other β -lactams, except ceftazidime, with which it shares a common R-group side chain. (B) The degree of cross-reactivity between penicillin and carbapenems appears to be low. (C) Diagnosis of IgE-mediated reactions to non- β -lactam antibiotics is limited by a lack of knowledge of the relevant allergenic determinants and/or metabolites. (C) Aspirin and nonsteroidal anti-inflammatory drugs are the second most common cause of drug-induced anaphylaxis. (C) Anaphylactic reactions to aspirin and other nonsteroidal anti-inflammatory drugs appear to be medication-specific. (D)

Anaphylactic reactions to omalizumab have occurred, and postmarketing data indicate that there is an incidence of approximately 0.2% in treated patients. These reactions have been unusual in that they can be delayed in onset and progressive. (C) On the basis of the fact that anaphylactic reactions to omalizumab can be delayed, an observation period of 2 hours for the first 3 injections and 30 minutes for subsequent injections is indicated. (D) All patients receiving omalizumab should be prescribed an automatic epinephrine injector and instructed in its use. Physicians should ensure that patients have such an injector with them at the time of the visits to the office for injection. (D) A preassessment (before the injection of omalizumab) of the patient's current health status should be made. This should include vital signs, an assessment of asthma control, and a measurement of lung function. (D)

Insect sting anaphylaxis

Anaphylaxis to insect stings has occurred in 3% of adults and 1% of children who have been stung and can be fatal even on the first reaction. (B) Cutaneous systemic reactions are more common in children, hypotensive shock is more common in adults, and respiratory complaints occur equally in all age groups. (B) The chance of a systemic reaction to a sting is low (5% to 10%) in patients who have large local reactions and in children with mild (cutaneous) systemic reactions. (A) Recurrence rates of reactions in adults vary between 25% and 70% depending on the severity of the previous systemic sting reaction. (A)

Venom skin tests are most accurate for diagnosis, but *in vitro* testing is an important complementary test. (A) The degree of sensitivity on skin or *in vitro* tests does not reliably predict the severity of a sting reaction. (B) Because asymptomatic venom sensitization can be detected in up to 25% of adults, diagnosis cannot be made on skin testing alone; the history is essential. (C) Patients discharged from emergency care for anaphylaxis should be given

autoinjectable epinephrine, receive instruction in its proper use and indications for use, and be advised to set up an appointment with an allergist-immunologist. Patients should understand, however, that using autoinjectable epinephrine is not a substitute for emergency medical attention. (A) Venom immunotherapy should be recommended for patients with systemic sensitivity to stinging insects because this treatment is highly (90% to 98%) effective. (B) Most patients can discontinue venom immunotherapy after 5 years with low residual risk (<10%) of a severe sting reaction. (A) 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 venom immunotherapy. (D) In a retrospective study of patients experiencing anaphylaxis from hymenoptera venom, Angiotensin Converting Enzyme (ACE) inhibitor exposure was associated with a statistically significant increase in risk for more severe anaphylaxis (odds ratio, = 2.27; 95% CI, 1.13-4.56; $P = .019$). For patients who require an ACE inhibitor for an indication for which there is no equally effective alternative available, a management decision by the physician prescribing venom immunotherapy should be approached cautiously on an individualized risk-benefit basis.

Prevention of anaphylaxis

While atopy may be a risk factor for seminal fluid anaphylaxis, venom-induced and latex-induced anaphylaxis, and possibly anaphylactic reactions to radiographic contrast material, it does not appear to be a risk factor for anaphylactic reactions to medications. (C) Avoidance management should be individualized, taking into consideration factors such as age, activity, occupation, hobbies, residential conditions, access to medical care, and the patient's level of personal anxiety. (C) Even in cases in which the allergen is known, avoidance measures may not always be successful. Therefore, patients should be instructed in self-management of anaphylaxis. (C) When avoidance is ineffective or not possible, other approaches can be used. For example, venom immunotherapy is successful in preventing anaphylaxis in up to 98% of patients who have previously experienced venom-induced anaphylaxis. (A) Pharmacologic prophylaxis should be used in select situations, such as to prevent recurrent anaphylactic reactions to radiographic contrast material and fluorescein, as well as to prevent idiopathic anaphylaxis. In these specific situations, prophylaxis with glucocorticosteroids and antihistamines markedly reduces the occurrence of subsequent reactions. (C) Desensitization to medications that are known to have caused anaphylaxis can be effective. The desensitization is temporary, and if the medication is required in the future, the desensitization process must be repeated. (C) Patient education might be the most important preventive strategy. Education can emphasize hidden allergens, cross-reactivity between various allergens and drugs, unforeseen risks during medical procedures, and when and how to use self-administered epinephrine. Physicians should educate patients about the risks of future anaphylaxis as well as the benefits of avoidance measures. (B) Patients at increased risk for anaphylactic events, such as those with allergy to insect venom, should avoid drugs that might increase their susceptibility and/or complicate the management of an anaphylactic event. (C)

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CLASSIFICATION OF RECOMMENDATIONS AND EVIDENCE**Category of evidence**

Ia Evidence from meta-analysis of randomized controlled trials
Ib Evidence from at least one randomized controlled trial

Iia Evidence from at least one controlled study without randomization

Iib Evidence from at least one other type of quasiexperimental study

III Evidence from non-experimental descriptive studies, such as comparative studies

IV Evidence from expert committee reports or opinions or clinical experience of respected authorities or both

Strength of recommendation

A Directly based on category I evidence

B Directly based on category II evidence or extrapolated recommendation from category I evidence

C Directly based on category III evidence or extrapolated recommendation from category I or II evidence

D Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence

LB (Lab Based)

PREFACE

This is the third iteration of this parameter entitled “The Diagnosis and Management of Anaphylaxis.” The first Anaphylaxis Parameter was published in 1998, and the second in 2005. Only the Preface, Significant New Developments, and the Executive Summary are in the printed version of this update. The entire document is available online and the reader is referred to that portion of the document for more detailed discussion of the comments made in the printed version.

The objective of this parameter is to improve the care of patients by providing the practicing physician with an evidence-based approach to the diagnosis and management of anaphylactic reactions.

The basic format of the document has remained unchanged. There are two algorithms: one on the evaluation of the patient who presents to the physician's office with a previous episode of anaphylaxis or a condition simulating an anaphylactic event, and the other on the suggested management of an episode occurring in the office. Only minor revisions have been made in these algorithms.

The annotations explaining the steps of the algorithms have been modestly altered in order to include more recent diagnostic tests and potential therapies. This edition retains all of the sections in the previous version including Anaphylaxis to Foods, Latex-Induced Anaphylaxis, Anaphylaxis during the Perioperative Period, Seminal Fluid Anaphylaxis, Exercise-Induced Anaphylaxis, Idiopathic Anaphylaxis, Anaphylaxis to Immunotherapy Vaccines, Anaphylaxis to Drugs, and the Prevention of Anaphylaxis. In addition, a new section on Hymenoptera Sting-Induced Anaphylaxis has been added. The section on Anaphylaxis to Drugs has also been expanded with a new section devoted to anaphylactic reactions to omalizumab and other biologic agents.

As always, the Joint Task Force on Practice Parameters and the contributing authors wish to thank the ACAAI, AAAAI, and JCAAI, for their continued support of parameter development. The Task Force would also like to thank the contributors to this parameter who have been so generous of their time and effort.

SIGNIFICANT NEW DEVELOPMENTS

A meeting of experts in the field of allergy and immunology held at the NIH in 2006 developed a definition of anaphylaxis as one of three clinical scenarios: 1) the acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue or both and at least one of the following: a) respiratory compromise; b) or reduced blood pressure or symptoms of end-organ dysfunction; 2) two or more of the following that occur rapidly after exposure to a likely allergen for that patient – involvement of the skin/mucosal tissue, respiratory compromise, reduced blood pressure or associated symptoms and/or persistent gastrointestinal symptoms; or 3) reduced blood pressure- after exposure to a known allergen. (1n)

The World Allergy Organization has suggested that the term “anaphylactoid reaction” be eliminated, and that all episodes clinically similar to IgE-mediated reactions be called anaphylaxis. They recommended that anaphylaxis be divided into immunologic and non-immunologic reactions, the latter being synonymous with the older term, “anaphylactoid,” and that immunologic reactions be divided into those mediated by IgE-mast cell/basophil mediator release and those occurring through other immunologic mechanisms (e.g., certain transfusion reactions). (2n) In this document, anaphylaxis will continue to mean an IgE-mediated reaction and non-IgE mediated reactions producing the same clinical response will be referred to as anaphylactoid.

A group of international experts was convened to determine the prevalence of anaphylaxis. The best data come from the number of prescriptions for automatic epinephrine injectors. Using these data, they came to the conclusion that the prevalence may be as high as 2%. (3n) It is now clear, from a number of recent studies, that the prevalence is rising, perhaps most markedly in the younger age group. (4n) Data also suggest- that there has been an increase in fatalities (4n-6n) and an increase in hospitalizations from anaphylaxis. (7n-10n)

There are data providing greater insight into the frequency of biphasic reactions. - More than one injection may be required to treat a biphasic or protracted reaction. (11n) Biphasic reactions are thought to increase the risk of fatal anaphylaxis. (12n-13n)

Anaphylactic reactions are not the sole result of immediate hypersensitivity mast cell/basophil derived mediators such as histamine, leukotrienes, and prostaglandins. Other mediator cascades are recruited (e.g., clotting and complement) including non-mast cell derived mediators which are responsible for many of the symptoms that occur in anaphylactic reactions. (14n) Consistent with these findings, there have been reports of patients not responding to “classical therapy” with epinephrine, but improving after the administration of agents such as tranexamic acid (if anaphylaxis is associated with intravascular coagulation) (15n) and methylene blue (if anaphylaxis is associated with hypotension). (16n)

Severe and fatal anaphylactic events can be related not only to the amount of mediators released, but also to the rapidity of their degradation. This concept has only thus far been confirmed for platelet activating factor. Patients with lower levels of platelet activating factor hydrolase (the enzyme that catabolizes platelet activating factor) are more susceptible to severe and even fatal reactions than patients with higher levels of this hydrolase. (17n) A correlation with decreased serum ACE levels has also been proposed. (18n)

Newer markers for anaphylaxis have been evaluated in hopes that they may enhance the diagnostic accuracy obtained from measuring tryptase, histamine, and their metabolites alone. In this regard the measurement of carboxypeptidase has shown great promise. (19n)

Patients who become hypotensive should remain recumbent until the cardiovascular system has been stabilized and they are completely asymptomatic. Deaths documented with regard to assuming the upright sitting position prematurely have occurred. (20n)

The standard needle length found on automatic epinephrine injectors may be insufficient to enable penetration into the vastus lateralis muscle (lateral thigh) in individuals having a large amount of subcutaneous fat overlying this muscle. (21n, 22n)

Insufficient use of epinephrine in children and adults has been documented in regard to ER treatment, as well as inadequate prescriptions for auto-injectable epinephrine, and referral to allergists-immunologists. (23n-25n)

It has recently been re-emphasized that an anaphylactic reaction to an insect sting may indicate an underlying mast cell disorder. In a recent article, 34 of 379 patients who developed anaphylaxis to an insect sting had indolent systemic mast cell disease or monoclonal mast cell activation syndrome on bone marrow biopsy, underlining previous recommendations that anaphylaxis be considered as a possible presentation for mast cell disease. (26n)

Anaphylaxis can present as an acute cardiac event (27n, 28n) and without dermatologic manifestations. (29n) In a retrospective analysis of anaphylaxis over a ten year period, 15% presented with chest pain and 7% presented with an arrhythmia. (5n) It has also been shown that there are abundant mast cells in the human heart and that the number and density of these cells is increased in patients with ischemic heart disease and dilated cardiomyopathies. (30n)

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ANNOTATIONS – FIG E1

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 may 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 either the upper airway or the lower airway?

- (3) Were there gastrointestinal symptoms, i.e., nausea, vomiting, diarrhea?
- (4) Were syncope or presyncopal symptoms present?

The absence of cutaneous symptoms puts the diagnosis in question since the majority of anaphylactic episodes include cutaneous symptoms (Table E1), 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, can often be useful in evaluating the history, physical findings, and treatment of the clinical event. In addition, the results of any previous laboratory studies (e.g., serum tryptase) may be helpful in making the diagnosis of anaphylaxis or distinguishing it from other entities.

Annotation 1A: Consider consultation with allergist/immunologist

Evaluation and diagnosis, as well as long-term management, can be complex. The allergist/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/immunology specialist.

Annotation 2: Pursue other diagnoses or make appropriate referral

Other conditions that should be considered in the differential diagnosis include: (1) vasodepressor (vasovagal/neuro-cardiogenic) syncope; (2) syndromes that can be associated with flushing (e.g., metastatic carcinoid); (3) postprandial syndromes (e.g., scombroid poisoning); (4) systemic mastocytosis; (5) psychiatric disorders that can mimic anaphylaxis such as panic attacks or vocal cord dysfunction syndrome; (6) angioedema (e.g., hereditary angioedema); (7) other causes of shock (e.g., 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 over the four to six hours prior to 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 since a substance added to the food could be responsible. A history of any preceding bite or sting should be obtained. The patient's activities (e.g., exercise, sexual activity) preceding the event should be reviewed. Patient diaries may 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 or *in vitro* tests, challenge tests?

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

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

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

Testing or challenge with reagents to a suspected allergen may not be available, or the predictive value of the test may be in question. Challenge tests (and, to a lesser extent, skin tests) may be hazardous, and not acceptable from a benefit: risk standpoint, if other management options are available. Occasionally patients may 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 (e.g., penicillin and insulin), and stinging insects as a cause of anaphylaxis. For the majority of 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 (e.g., penicillin and insect stings). It is essential, however, 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 (e.g., latex, protamine, or antibiotics other than penicillin), the clinical relevance of the results may be uncertain. If skin testing is performed, 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 (i.e., skin tests, *in vitro* tests, or both) do not provide conclusive evidence of the cause of anaphylaxis, challenge with the suspected agent can be considered. Challenge procedures may also be appropriate in patients who develop non-IgE-mediated reactions (e.g., reactions to aspirin (ASA) or other nonsteroidal anti-inflammatory drugs (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 may be helpful include: serum tryptase, as well as urinary 5-hydroxyindoleacetic acid, methylhistamine, 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 may be supported by the results of skin tests, *in vitro* IgE tests, and/or challenge tests (particularly double-blind, placebo-controlled challenge tests).

Annotation 10: Management of anaphylaxis

When anaphylaxis has occurred because of exposure to a specific agent (e.g., 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 may be used to reduce 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 may be helpful to educate patients about applicable management options (e.g., medication pretreatment and use of low osmolarity agents in patients with a history of reactions to radiographic contrast media 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 reduce the risk of an insect sting and usually are candidates for insect venom immunotherapy. Patients who have had anaphylaxis should carry self-injectable epinephrine if there is continued risk for anaphylaxis. Patients should also carry identification indicating that they have experienced anaphylaxis and indicating the responsible agent.

ANNOTATIONS – FIG E2**Annotation 1. Anaphylaxis Preparedness**

Management recommendations are subject to physician discretion as well as practice resources and the proximity to emergency assistance. Variations in sequence and performance rely on physician judgment. A determination of when a patient should be transferred to an emergency facility depends on the skill, experience and clinical decision-making of the individual physician. Prompt recognition and appropriate, aggressive treatment are essential for the successful management of anaphylaxis.

Stocking and maintaining supplies for the treatment of anaphylaxis with regular written documentation of supplies and expiration dates and ready availability of injectable epinephrine, intravenous fluids and needles, oxygen and mask/cannula, airway adjuncts, and stethoscope and sphygmomanometer are bare

essentials. (An example of a supply checklist is included in Section VI, “Management of Anaphylaxis”)

Regular anaphylaxis practice drills, the makeup of which is left to the discretion and qualifications of the individual physician, are strongly recommended. It is essential to identify a person who will be responsible for calling emergency medical services and the person who will document each treatment and the time that each is rendered. Emergency medications should be up-to-date and complete. Everyone who will be directly involved in patient care should be able easily to locate necessary supplies, rapidly assemble fluids for intravenous administration, and be prepared to begin treatment so that no time is lost in implementing emergency measures.

Annotation 2. Patient Presents with Possible/ Probable Acute Anaphylaxis

Anaphylaxis is an acute life-threatening reaction, usually but not always mediated by an immunologic mechanism, that results from the sudden systemic release of mediators from mast cells and basophils. Anaphylaxis has varied clinical presentations but respiratory compromise and cardiovascular collapse are of greatest concern, since they are the most frequent causes of fatalities. Urticaria and angioedema are the most common manifestations of anaphylaxis but may be delayed or absent especially in rapidly progressive anaphylaxis. The more rapid anaphylaxis occurs after exposure to an offending stimulus, the more likely the reaction is to be severe and potentially life-threatening.

Anaphylaxis often produces signs and symptoms within minutes of exposure to an offending stimulus but some reactions may develop later (e.g., greater than 30 min after exposure). Late phase or “biphasic” reactions, which occur 1 to 72 hr (most within 10 hr) after the initial attack, have also been reported. Protracted, severe anaphylaxis may last up to 32 hr despite aggressive treatment.

Increased vascular permeability, a characteristic feature of anaphylaxis, allows transfer of as much as 35% of the intravascular fluid into the extravascular space within 10 min. As a result, hemodynamic collapse may occur rapidly with little or no cutaneous or respiratory manifestations.

Annotation 3. Initial Assessment of Possible/ Probable Anaphylaxis

Initial assessment should determine if history and physical findings are compatible with anaphylaxis. The setting of the episode and the past history may suggest or reveal the source of the reaction. Evaluation should include: level of consciousness (impairment may reflect hypoxia), upper and lower airways (dysphonia, stridor, cough, wheezing, shortness of breath), cardiovascular system (hypotension with or without syncope; and/or cardiac arrhythmias), the skin (diffuse or localized erythema, pruritus, urticaria and/or angioedema), and the gastrointestinal system (nausea, vomiting, diarrhea). In addition, some patients may have symptoms of lightheadedness, headache, uterine cramps, feeling of impending doom, and unconsciousness.

The vasodepressor (vaso-vagal) reaction probably is the condition most commonly confused with anaphylactic reactions. In vasodepressor reactions, however, urticaria is absent, the heart rate is typically bradycardic, bronchospasm or other breathing difficulty is generally absent, the blood pressure is often

decreased when accompanied by symptomatic bradycardia but it may be normal, and the skin is typically cool and pale. While tachycardia is the rule, bradycardia may occur during anaphylaxis, so bradycardia may not be as useful to separate anaphylaxis from a vasodepressor reaction as has previously been thought. Relative bradycardia (initial tachycardia followed by a reduction in heart rate despite worsening hypotension) has been reported previously in the setting of experimentally induced insect sting anaphylaxis and in other states of hypovolemia (e.g., trauma). Tachycardia may also be absent in patients with conduction defects, increased vagal tone due to a cardioinhibitory (Bezold-Jarisch) reflex, or in those who take sympatholytic medications.

Annotation 4. Consider Other Diagnosis

Other diagnoses that might present with signs and/or symptoms characteristic of anaphylaxis should be excluded. Among conditions to consider are vasodepressor (vasovagal) reactions, vocal cord dysfunction, acute anxiety (e.g., panic attack or hyperventilation syndrome), myocardial dysfunction, pulmonary embolism, foreign body aspiration, acute poisoning, hypoglycemia, and seizure disorder. Specific signs and symptoms of anaphylaxis may be in other disorders such as urticaria/angioedema, and asthma.

Annotation 5. Immediate Intervention

Anaphylaxis occurs as part of a continuum. Symptoms not immediately life-threatening may progress rapidly unless treated promptly. Treatment recommendations are subject to physician discretion and variations in sequence and performance rely on physician judgment. Additionally, a determination of when a patient should be transferred to an emergency or intensive care facility depends on available resources and the skill, experience and clinical decision-making of the individual physician.

- a) Assess airway, breathing, circulation, and level of consciousness (altered mentation may suggest the presence of hypoxia).
- b) Administer epinephrine. Aqueous epinephrine 1:1000 dilution (1 mg/ml), 0.2-0.5 ml (0.01 mg/kg in children, max 0.3 mg dosage) intramuscularly in the lateral aspect of the thigh or subcutaneously every 5 min, as necessary, to control symptoms and increase blood pressure. If the clinician deems it appropriate, the 5-minute interval between injections can be liberalized to permit more frequent injections. Intramuscular epinephrine injections into the thigh have been reported to provide more rapid absorption and higher plasma epinephrine levels in both children and adults than intramuscular or subcutaneous injections administered in the arm. However, similar studies comparing intramuscular injections to subcutaneous injections in the thigh have not been done. These studies were not performed in patients experiencing anaphylaxis. The generalizability of these findings to the clinical setting of anaphylaxis has not been established. There are no studies that support the use of epinephrine in the treatment of anaphylaxis when delivered by a non-parenteral route. However, alternative routes of administration have been anecdotally successful. These include, for example, inhaled epinephrine in the presence of laryngeal edema or sublingual administration if an intravenous route cannot be obtained. Endotracheally administered dosages have also been proposed for use when intravenous

access is not available in intubated patients experiencing cardiac arrest.

Annotation 6. Subsequent Measures That May Be Necessary Depending on Response to Epinephrine

- a) Consider calling 911 and obtaining assistance.
- b) Place the patient in a recumbent position and elevate the lower extremities, as tolerated symptomatically. This slows progression of hemodynamic compromise, if present, by preventing orthostatic hypotension and helping to shunt effective circulation from the periphery to the head, the heart and kidneys.
- c) Establish and maintain an airway. Ventilatory assistance via a one-way valve facemask with oxygen inlet port (e.g., Pocket-Mask^R or similar device) may be necessary. Bag valve masks of less than 700 ml are discouraged in adults in the absence of an endotracheal tube since ventilated volume will not overcome 150-200 ml of anatomic dead space to provide effective tidal volume. (Bag valve masks may be used in children provided the reservoir volume of the device is sufficient.) Endotracheal intubation or cricothyroidotomy may be considered where appropriate, provided clinicians are adequately trained and proficient in this procedure.
- d) Administer oxygen. Oxygen should be considered for patients with anaphylaxis who have prolonged reactions, have pre-existing hypoxemia or myocardial dysfunction, receive inhaled β -agonists as part of the treatment for anaphylaxis, or who require multiple doses of epinephrine. Continuous pulse oximetry and/or arterial blood gas determination (where available) should guide oxygen therapy, especially in high risk patients, e.g. patients with COPD.
- e) Rapid intravenous fluid replacement should be started when the patient has failed to respond to the treatment as outline above. Administration and dosage of intravenous fluids are discussed under the section on "Anaphylaxis Treatment".
- f) Consider diphenhydramine, 1-2 mg/kg or 25-50 mg/dose (parenterally). H1 antihistamines are considered second-line to epinephrine and should not be administered in lieu of epinephrine in the treatment of anaphylaxis.
- g) Consider ranitidine, 50 mg in adults and 12.5-50 mg (1 mg/kg) in children, which may be diluted in 5% dextrose to a total volume of 20 ml and injected IV over 5 min. Cimetidine (4 mg/kg) may be administered IV to adults, but no pediatric dosage for the treatment of anaphylaxis has been established. In the management of anaphylaxis, a combination of diphenhydramine and ranitidine is superior to diphenhydramine alone. However, these agents have a much slower onset of action than epinephrine and should never be used alone in the treatment of anaphylaxis. Both alone and in combination these agents are second-line to epinephrine.
- h) Consider inhaled β -agonist (e.g., albuterol MDI 2-6 puffs or nebulized, 2.5-5 mg in 3 ml saline and repeat as necessary) for bronchospasm resistant to adequate doses of epinephrine.
- i) Glucocorticosteroids should never be used in place of or prior to epinephrine and are not helpful acutely. However, they have the potential to prevent recurrent or protracted anaphylaxis.

Annotation 7. Subsequent Measures That May Be Necessary Depending on Response to Epinephrine

When anaphylaxis is not responding to the above measures, including repeated doses of IM or SQ epinephrine, the use of IV epinephrine, vasopressors and glucagon may need to be considered. (See section on Anaphylaxis Treatment.)

Annotation 8. Interventions for Cardiopulmonary Arrest Occurring during Anaphylaxis

- a) Cardiopulmonary resuscitation and advanced cardiac life support measures.
- b) High-dose epinephrine IV (i.e., rapid progression to high dose). A common sequence is 1 to 3 mg (1:10,000 dilution) IV slowly administered over 3 min, 3 to 5 mg IV over 3 min, and then 4-10 μ g/min infusion. For children, the recommended initial resuscitation dosage is 0.01 mg/kg (0.1 ml/kg of a 1:10,000 solution up to 10 μ g/min rate of infusion), repeated every 3 to 5 min for ongoing arrest. Higher subsequent dosages (0.1-0.2 mg/kg; 0.1 ml/kg of a 1:1,000 solution) may be considered for unresponsive asystole or pulseless electrical activity (PEA).
- c) Rapid volume expansion.
- d) Atropine if asystole or pulseless electrical activity (PEA) is present.
- e) Prolonged resuscitation is encouraged, if necessary, since a successful outcome is more likely in anaphylaxis.
- f) Transport to emergency department or intensive care, as setting dictates.

Annotation 9. Observation and Subsequent Follow-Up

Biphasic anaphylaxis occurs in 1% to 23% of episodes of anaphylaxis, and symptoms may recur hours (most within 10 hours) after apparent resolution of the initial phase. However, observation periods must be individualized since there are no reliable predictors of biphasic or protracted anaphylaxis based on initial clinical presentation. Similarly, follow-up must be individualized and based on distance from patient's home to closest emergency facility, severity of the reaction, patient's response to treatment, and other factors. Following resolution of the acute episode, patients should be provided with autoinjectable epinephrine and receive proper instruction for self-administration in case of a subsequent episode. In circumstances where an allergist-immunologist is not already involved, it is strongly recommended that individuals who have experienced acute anaphylaxis should be referred to an allergist-immunologist for consultation regarding diagnosis, prevention, and treatment.

Annotation 10. Consultation with Allergist-Immunologist

After acute anaphylaxis is resolved, patients should be assessed for future risk of anaphylaxis. The allergist-immunologist can obtain a detailed history, coordinate allergy diagnostic testing, evaluate the risks and benefits of therapeutic options, train the patient in self-administration of epinephrine, and provide counseling on avoidance measures, which is the most effective treatment for most causes of anaphylaxis.

EVALUATION AND MANAGEMENT OF PATIENTS WITH A HISTORY OF ANAPHYLAXIS

Summary Statements

1. The history is the most important tool to determine whether a patient has had anaphylaxis and the cause of the episode. C
2. A thorough differential diagnosis should be considered, and other conditions should be ruled out. C
3. Laboratory tests can be helpful to confirm a diagnosis of anaphylaxis or rule out other causes. Proper timing of such tests (e.g., serum tryptase) is essential. B
4. In the management of a patient with a previous episode of anaphylaxis, education is necessary. Emphasis on early treatment, specifically the self-administration of epinephrine, is essential. C
5. The patient can be instructed to wear and/or carry identification denoting his or her condition (e.g., Medic Alert jewelry), and can also be instructed to have telephone numbers for paramedic rescue squads and ambulance services on hand. A written action plan can be helpful in this regard. C

Performing the History

To interpret the history adequately it is essential to know the manifestations of anaphylaxis. These can best be ascertained by a review of published series on the topic.¹⁻¹² A summary of the signs and symptoms as reported in these series, totaling 1,865 patients, is seen in Table E1. These series include patients of all ages suffering from exercise-induced anaphylaxis, idiopathic anaphylaxis, and from various other causes. The most frequent manifestations of anaphylaxis are cutaneous, occurring in over 90% of reported series. 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.^{13,15} To better assess the signs and symptoms of the reaction, friends and/or family members present during the event may sometimes need to be interviewed. Anaphylaxis can present with unusual manifestations, e.g., syncope without any other sign or symptom.^{13,15} Additionally, based on studies limited to children, the incidence of cutaneous manifestations in children may be lower.¹⁶⁻¹⁷

The history and the record should include the time of the occurrence of the attack, the setting in which it occurred, any treatment required during the attack, 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 six hours of the event, any sting or bite occurring prior to the event, if the event occurred during exercise, location of the event (e.g., work versus home), and whether or not the event was related to exposure to heat, cold, or occurred during sexual activity. The patient's atopic status should be noted since food-induced, seminal fluid and idiopathic anaphylaxis are more common in atopic than non-atopic individuals. In women, the history should include any relationship between the attack and their menstrual cycle. A return of symptoms following a remission should be noted since this may indicate a late phase reaction,¹⁸ which might require a prolonged period of observation if subsequent events occur.

Differential Diagnosis

The differential diagnosis must be considered whenever the history is taken, even in patients with a previous history of anaphylaxis. A comprehensive differential diagnosis is seen in Table E2. 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 can often be distinguished from anaphylaxis by a lack of characteristic cutaneous manifestations (urticaria, angioedema, flush, 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 as well¹⁹. 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.¹⁹

Flushing episodes can mimic anaphylactic events. Several drugs and ingestants including niacin, nicotine, catecholamines, ACE inhibitors, and alcohol can induce flushing²⁰. 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" due to the administration of vancomycin. Laboratory studies (Table E3) can be helpful in establishing if the patient is experiencing anaphylaxis.

There are a group of postprandial syndromes that can mimic anaphylaxis, such as monosodium glutamate-induced reaction, and reactions to scombroid fish. The latter is increasing in frequency²¹ and since 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 may be more of a flush (sunburn-like) than urticaria. Symptoms may affect more than one individual if they also ingested the fish causing the reaction and serum tryptase levels are normal.

Laboratory Studies

Laboratory studies to be considered are seen in Table E3. Serum tryptase and plasma and urinary histamine levels can sometimes be helpful in establishing the diagnosis of anaphylaxis.²²⁻³¹ Plasma histamine levels begin to rise within 5 to 10 minutes of the onset of symptoms of anaphylaxis and remain elevated for 30 to 60 minutes.^{25,27} Therefore, they are not of help if the patient is seen as long as an hour or more after the onset of the event.²⁸ However urinary methyl-histamine levels are elevated for a longer duration of time.²⁹ Serum tryptase levels peak one to one and one-half hours after the onset of anaphylaxis and can persist for as long as five hours after the onset of symptoms.²⁵ The best time to measure serum tryptase is between one to two hours but no longer than six hours after the onset of symptoms.²⁵ The best time to measure plasma histamine is between 10 minutes and one hour after the onset of symptoms.²⁵ It should be noted that there can be a disconnection between histamine and tryptase levels with some patients exhibiting elevation of only one of these mediators.^{24,25}

It was originally thought that tryptase was present in an alpha and β form, and that alpha tryptase comprised the majority of constitutively secreted tryptase. Subjects with null alleles for alpha tryptase exhibited “normal” levels of tryptase. It is now known that constitutively secreted tryptase is, for the most part, β -pro tryptase (immature β tryptase) with alpha tryptase contributing only a small, negligible amount.²⁶ Upon mast cell degranulation there is a marked increase in tryptase which is composed of mature β tryptase. Thus, constitutively secreted tryptase is a mixture of alpha (in modest amounts) and β -pro tryptase (immature tryptase) (the majority amount). Marked increases in total tryptase are seen during an anaphylactic event. This is due to the rise in mature β tryptase released only during degranulation.²⁷

It has been proposed that elevations of postmortem serum tryptase be used to establish anaphylaxis as a cause of death.²⁸ 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.²⁹⁻³¹ Thus, the presence of an elevated postmortem tryptase level cannot be considered pathognomonic for a death due to anaphylaxis. Nor can an absence of an elevated serum tryptase postmortem be considered sufficient to rule out anaphylaxis as the cause of death.²⁹ In patients with a possible anaphylactic reaction to food, leftover or vomited food may be useful as a source of antigen for the creation of an in-vitro test reagent.²⁸

Total tryptase levels can be elevated in conditions other than mastocytosis and anaphylaxis, such as acute myelocytic leukemia, hyper eosinophilic syndrome associated with the FIP1 L1-PDGFR mutation, myelodysplastic syndromes, and end-stage renal disease with endogenous stem cell factor elevation.²² Because of this, other markers for mast cell degranulation are being evaluated. Particularly promising is mast cell carboxypeptidase A3. Also being studied are platelet activating factor and chymase.³² It is of note that platelet activating factor and its hydrolase are both measurable and that the severity of anaphylaxis is directly correlated with serum levels of platelet activating factor and inversely correlated with serum levels of platelet activating factor hydrolase.

If a patient has had a previous episode of anaphylaxis, the patient needs to be educated about the need for early treatment of any subsequent episodes, in particular, the self-administration of epinephrine. Patients who have experienced an episode of anaphylaxis can also carry identification denoting their possible susceptibility to future episodes. This can consist of a card and/or identification jewelry (e.g., Medic Alert).

Medical facilities should have an established protocol to manage anaphylaxis and the appropriate equipment to treat an anaphylactic reaction. In addition, telephone numbers for paramedical rescue squads and ambulance services might be helpful to have on hand.

OFFICE MANAGEMENT OF ANAPHYLAXIS

Summary Statements

- 6. Anaphylaxis is an acute, life-threatening systemic reaction with varied mechanisms, clinical presentations, and severity that results from the sudden systemic release of mediators from mast cells and basophils. B**
- 7. The more rapidly anaphylaxis develops, the more likely the reaction is to be severe and potentially life-threatening. C**

- 8. Prompt recognition of signs and symptoms of anaphylaxis is crucial. If there is any doubt, it is generally better to administer epinephrine. C**
- 9. Epinephrine and oxygen are the most important therapeutic agents administered in anaphylaxis. Epinephrine is the drug of choice, and the appropriate dose should be administered promptly at the onset of apparent anaphylaxis. The consensus of experts is that, in general, treatment in order of importance is: epinephrine, patient position, oxygen, intravenous fluids, nebulized therapy, vasopressors, antihistamines, corticosteroids, and other agents. C**
- 10. Appropriate volume replacement either with colloid or crystalloids and rapid transport to the hospital is essential for patients who are unstable or refractory to initial therapy for anaphylaxis in the office setting. B**
- 11. Medical offices and facilities in which anaphylaxis is possible should have a well established plan of action to deal with anaphylaxis that is regularly practiced and the appropriate equipment to treat anaphylaxis. The more rapid the treatment, the better the outcome. Therefore, personnel in a medical office dealing directly with the patient's medical care should be familiar with the manifestations of anaphylaxis and be able to recognize an event quickly. Access to therapy should be immediately available. B**
- 12. Physicians and office staff should maintain clinical proficiency in anaphylaxis management. D**
- 13. In addition, telephone numbers for paramedical rescue squads and ambulance services might be helpful to have on hand. C**

The management of anaphylaxis is summarized in algorithmic form in Fig E2. Appropriate management requires adequate supplies, and a list of these supplies is noted in Fig E3. The following equipment and supplies should be available:³³⁻³⁵ (1) Stethoscope and sphygmomanometer; (2) injectable aqueous epinephrine 1:1000; (3) oxygen and equipment for administering it; (4) intravenous fluids and equipment for administering them, and (5) tourniquets, syringes, hypodermic needles, large-bore needles (e.g., 14- or 16-gauge); The following equipment and supplies should be considered depending on the availability of emergency support services (1) one-way valve facemask with oxygen inlet port (e.g., Pocket-Mask™ or similar device); (2) diphenhydramine or similar injectable antihistamine; (3) corticosteroids for intravenous injection; and possibly (4) a vasopressor (e.g., dopamine or norepinephrine). Some clinicians may strongly consider having available glucagon, an automatic defibrillator, and/or oral airway depending on the clinical setting.

EPINEPHRINE

The initial drug of choice is epinephrine.³³⁻³⁷ The following are salient points regarding administration of epinephrine:

- The concentration is 1:1000 and the adult dose is 0.2 to 0.5 ml (mg). The dose in a child is 0.01 ml (mg)/kg.**
- The time to highest blood concentration (C_{max}), when studied in asymptomatic subjects, is shorter when injection is given intramuscularly in the vastus lateralis muscle (lateral thigh) than when it is administered either subcutaneously or intramuscularly in the deltoid muscle of the arm. There are no outcome data comparing these**

routes of administration during anaphylaxis. There are no data indicating that epinephrine is ineffective when administered either subcutaneous or intramuscular in the deltoid muscle of the arm.

- Epinephrine may be administered every 5 to 10 minutes as necessary. If the clinician deems it appropriate, the 5 minute interval between injections can be liberalized to promote more frequent administration.
- Epinephrine should be administered as soon as the diagnosis of anaphylaxis is suspected.
- Although the diagnosis of anaphylaxis usually depends on involvement of two organ systems (e.g., skin plus respiratory, skin plus cardiovascular), anaphylaxis may present as an acute cardiac or respiratory event or with hypotension as the only manifestation of anaphylaxis.
- The case of suspected anaphylaxis even if it involves only one system, such as the skin, epinephrine administration may be indicated.
- Intravenous administration may be considered in patients poorly responsive to intramuscular or subcutaneous epinephrine, where there is inadequate time for emergency transport or prolonged transport is required. No established dosage or regimen for intravenous epinephrine in anaphylaxis is recognized. However, a prospective study demonstrated the efficacy of a 1:100,000 solution of epinephrine (0.1 mg [1 ml of 1:1000] in 100 ml saline) intravenously by infusion pump at an initial rate of 30-100 ml/hr (5-15 $\mu\text{g}/\text{min}$), titrated up or down depending on clinical response or epinephrine side effects (toxicity). Inferences regarding intravenous dosing may also be drawn from the emergency cardiac care consensus guidelines for intravenous epinephrine for adults and children.^{37,38} An epinephrine infusion may be prepared by adding 1 mg (1 ml) of 1:1000 dilution of epinephrine to 250 ml of D5W to yield a concentration of 4.0 $\mu\text{g}/\text{ml}$. This 1:250,000 solution is infused at a rate of 1 $\mu\text{g}/\text{min}$ (15 drops/minute using a micro-drop apparatus [60 drops/minute = 1 ml = 60 ml/hr]), titrated to desired hemodynamic response, increasing to a maximum of 10.0 $\mu\text{g}/\text{min}$ for adults and adolescents. A dosage of 0.01 mg/kg (0.1 ml/kg of a 1:10,000 solution up to 10 $\mu\text{g}/\text{min}$; maximum dose, 0.3 mg) is recommended for children. Alternative pediatric dosage by the "Rule of 6" is, as follows: 0.6 X body weight (in kg) = # of mg diluted to total 100 ml saline; then 1ml/hr delivers 0.1 $\mu\text{g}/\text{kg}/\text{min}$.³⁹ (See Table E4 for infusion guidelines in children.) An alternative epinephrine infusion protocol has been suggested for adults with anaphylaxis.¹⁹
- Because of the risk of potentially lethal arrhythmias, epinephrine should be administered intravenously only in profoundly hypotensive patients or patients in cardio/respiratory arrest who have failed to respond to intravenous volume replacement and several injected doses of epinephrine. In situations where hemodynamic monitoring is available (e.g., emergency department, intensive care facility), continuous hemodynamic monitoring is recommended if epinephrine is given intravenously.¹⁹ However, use of intravenous epinephrine should not be precluded in a scenario where such monitoring is not available, if the clinician deems its administration is essential after several intramuscular/subcutaneous epinephrine injections. If

intravenous epinephrine is considered under these special circumstances, monitoring by available means (e.g., every-minute blood pressure and pulse measurements and ECG monitoring, if available) should be considered.

Numerous cases of unusually severe or refractory anaphylaxis have been reported in patients receiving β -adrenergic blockers.⁴⁰⁻⁵³ Although the pharmacology of provocation or exacerbation of bronchospasm with use of β -blockers is well known, the pharmacodynamics that contribute to greater risk for more serious anaphylaxis are not as widely recognized.⁵⁴⁻⁵⁶ These systemic effects have also been documented with use of ophthalmic β -blockers.⁵⁷ Greater severity of anaphylaxis observed in patients receiving β -blockers might relate, in part, to a blunted response to epinephrine administered to treat anaphylaxis.⁵⁷ 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.⁵⁸ In patients receiving β -blockers, increased propensity not only for bronchospasm, but also decreased cardiac contractility with perpetuation of hypotension and bradycardia might exist.⁵⁸⁻⁶⁰ For these reasons, β -blocker-related anaphylaxis may be more likely to be refractory to management. There are no epidemiologic studies that indicate that anaphylaxis occurs more frequently in patients receiving β -blockers. In view of β -blocker withdrawal syndromes observed in selected cases and the clear benefits that may accrue from use of β -blockers in patients for whom these drugs are indicated, the decision to withhold or discontinue β -blockers must be considered carefully from the perspective of risk vs. benefit for each individual.^{45-47,61-64} Therefore, patients taking β -blockers may be more likely to experience severe anaphylactic reactions characterized by paradoxical bradycardia, profound hypotension, and severe bronchospasm. Use of selective β_1 -antagonists does not reduce the risk of anaphylaxis because both β_1 and β_2 -antagonists may inhibit the β -adrenergic receptor.

If epinephrine is ineffective in treating anaphylaxis in patients taking β -blockers, both glucagon administration and isotonic volume expansion (in some circumstances, up to 7 L of crystalloid) may be necessary.^{53,65-69} Glucagon may reverse refractory bronchospasm and hypotension during anaphylaxis in patients on β -blockers by activating adenylyl cyclase directly and bypassing the β -adrenergic receptor.^{53,67-69} The recommended dosage for glucagon is 1 to 5 mg (20-30 $\mu\text{g}/\text{kg}$ [max. 1 mg] in children) administered intravenously over 5 min and followed by an infusion, 5-15 $\mu\text{g}/\text{min}$, titrated to clinical response. Protection of the airway is important since glucagon may cause emesis and risk aspiration in severely drowsy or obtunded patients. Placement in the lateral recumbent position may be sufficient airway protection for many of these patients.

POSITIONING OF PATIENT

Place the patient in a supine position and elevate the lower extremities, particularly when there is concern for hemodynamic compromise. This slows the progression of hemodynamic compromise by preventing orthostatic hypotension and helping to shunt effective circulation from the periphery to the head, the heart and kidneys. Patients who become hypotensive should remain recumbent until the cardiovascular system has been stabilized and they are completely asymptomatic.⁷⁰ Deaths have occurred if the patient assumes the upright sitting position prematurely.⁷¹

OXYGEN

Oxygen should be administered to patients with anaphylaxis who have prolonged reactions. Oxygen can be considered in any patient manifesting symptoms. Oximetry can be used to guide oxygen treatment.

FLUID RESUSCITATION

The patient whose hypotension persists despite epinephrine injections should receive intravenous crystalloid solutions or colloid volume expanders. Of available crystalloid solutions, saline is generally preferred in distributive shock (e.g., anaphylactic shock) because it stays in the intravascular space longer than dextrose and contains no lactate which may potentially exacerbate metabolic acidosis. Large volumes of fluid are often required, especially in patients taking a β -adrenergic blocking agent. One to 2 L of normal saline may need to be administered to adults at a rate of 5-10 ml/kg in the first 5 minutes. Children should receive up to 30 ml/kg in the first hour. Adults receiving colloid solution should receive 500 ml rapidly, followed by slow infusion. Caution for volume overload is advised if the patient has a history of congestive heart failure.

Clinicians who are adequately trained and proficient at obtaining intraosseous (IO) access for either adults or children may consider this approach if attempts at IV access have been unsuccessful. IO cannulation provides access to a non-collapsible venous plexus, which is attainable in all age groups and several studies have documented its safety and efficacy. Fluids administered IO for volume replacement should be infused under pressure using an infusion pump, pressure bag, or manual pressure to overcome venous resistance. Less than 1% of patients have complications after an IO infusion.^{72,73}

INHALED β_2 ADRENERGIC AGONISTS

For patients who develop bronchospasm, an inhaled β_2 agonist can be helpful, especially when bronchospasm does not respond to epinephrine. There is anecdotal evidence that inhaled epinephrine can be effective in anaphylaxis and that inhaled β_2 agonists might be helpful, especially for upper airway obstruction.

VASOPRESSORS

Vasopressors, such as dopamine (400mg in 500ml of 5% dextrose) administered at 2-20 $\mu\text{g}/\text{kg}/\text{min}$ and titrated to maintain systolic blood pressure greater than 90 mm Hg, should be administered if epinephrine injections and volume expansion fail to alleviate hypotension.⁷⁴ Dopamine will usually increase blood pressure while maintaining or enhancing blood flow to the renal and splanchnic circulation. In cases of intractable hypotension, transfer of the patient to a hospital, with an appropriate critical care environment, should be performed as soon as possible.

It has been shown that a dose of dopamine $> 10 \mu\text{g}/\text{kg}/\text{min}$ is usually required to produce peripheral vasoconstriction which would be required to maintain systolic blood pressure. After promising results in various animal models for cardiopulmonary resuscitation, vasopressin has been investigated for potential benefit in cardiac arrest in humans.⁷⁵⁻⁷⁷ In addition, there is one report evaluating the effectiveness of vasopressin on hypotension in two adults who experienced insect sting anaphylaxis and one report of a patient who received vasopressin after anaphylaxis to a drug.⁷⁸⁻⁷⁹

High quality randomized controlled trials have not demonstrated that vasopressin is more effective than epinephrine in the treatment of cardiac arrest.^{75-77,80} No controlled studies have been performed to evaluate the potential efficacy of vasopressin in anaphylaxis, alone or in combination with epinephrine.

H1 AND H2 ANTIHISTAMINES

Antihistamines are considered supportive therapy and do not replace epinephrine. Antihistamines are second line drugs that can be given after epinephrine administration since they may be useful for control of cutaneous and cardiovascular manifestations. The salient features regarding use of antihistamines are:

- **Diphenhydramine, an H1 antagonist, may be given IM or by slow intravenous infusion in a dose of 25 to 50 mg in adults, and 1 mg/kg up to 50 mg in children. Indirect evidence supports the parenteral administration of diphenhydramine and hydroxyzine. Oral diphenhydramine as well as other oral first or second generation H1 antihistamines can also be used. There is no direct outcome data regarding the effectiveness of any antihistamine in anaphylaxis.**⁸¹
- **An H2 antagonist added to the H1 antagonist may be helpful in the management of anaphylaxis.**^{19,81-87} Parenteral ranitidine can be considered in a dose of 1 mg/kg in adults, and 12.5 to 50 mg in children. Since time to maximum serum concentration (Cmax) is approximately the same for intravenous and intramuscular administration, either route can be considered. If intravenous administration is chosen, the drug should be infused over 10 to 15 minutes. It may also be diluted in 5% dextrose to a volume of 20 ml and injected over 5 minutes.

CORTICOSTEROIDS

Glucocorticosteroids have not been shown to be effective for the acute treatment of anaphylaxis but could, theoretically, prevent protracted anaphylaxis. There is no conclusive evidence that the administration of corticosteroids prevents a biphasic response.⁸⁸

OTHER PROPOSED THERAPIES FOR ANAPHYLAXIS

Several other therapeutic agents have been proposed for use in anaphylaxis. However, there is no high quality evidence that supports these agents, and existing data are too limited for consensus opinions to be reached.

- **Leukotriene modifiers:**
At this time there are no data documenting the efficacy of leukotriene modifiers in the treatment of anaphylaxis or in its prevention. In addition, at this time, the only available route of administration is oral and therefore the onset of action of such agents in anaphylaxis would not be optimal.
- **Tranexamic acid has been used to treat anaphylactic episodes associated with disseminated intravascular coagulation, however, it is not available in the United States.**⁸⁹
- **Nitric oxide synthesis inhibition via methylene blue has been reported, in case reports, to be helpful in the treatment of hypotension occurring during anaphylaxis. There are no controlled studies, however, involving the use of this agent in anaphylaxis.**⁹⁰

OBSERVATION AND SUBSEQUENT FOLLOW-UP

Biphasic anaphylaxis occurs in 1% to 23% of episodes, and symptoms may recur hours (most within 10 hours) after apparent resolution of the initial phase⁵. However, observation periods must be individualized since there are no consistently reliable predictors of biphasic or protracted anaphylaxis based on initial clinical presentation.

Follow-up of patients who have experienced anaphylaxis must be individualized and based on such factors as clinical scenario and distance from patient's home to closest emergency facility.

At the time of discharge from medical supervision, patients should be provided with autoinjectible epinephrine and instructed in its use. In circumstances where an allergist/immunologist is not already involved, it is strongly recommended that consultation with an allergist/immunologist be obtained.

An action plan is an important component of the follow-up of patients who have experienced anaphylaxis. Available resources may be an important consideration in determining the treatment plan that is appropriate for the setting in which the physician practices.⁹¹⁻⁹³ Examples of written action plans can be downloaded over the Internet (e.g., American Academy of Allergy, Asthma, and Immunology (www.aaaai.org/members/resources/anaphylaxis_toolkit/action_plan.pdf) [Spanish language versions of the following AAAAI anaphylaxis materials are available: the AAAAI Anaphylaxis Emergency Action Plan, Killer Allergy information page, AAAAI Anaphylaxis Tips to Remember brochure, and AAAAI Anaphylaxis Easy Reader page.]; Food Allergy and Anaphylaxis network [English language version: www.foodallergy.org/actionplan.pdf; Spanish language version: www.foodallergy.org/spanishaction.pdf; www.foodallergy.org/school/SchoolGuidelines.pdf]).

ANALYSIS OF ANAPHYLAXIS OUTCOMES AND PROCEDURES

Following treatment for any episode of acute anaphylaxis, the clinician should consider an analysis of the event and the possible precipitating cause, particularly with respect to those steps that could be done to prevent future episodes. (See Section on Prevention of Anaphylaxis.) The clinical staff can also critique the approach taken to manage anaphylaxis after each episode with regard to what worked well and what needs improvement.

ANAPHYLAXIS TO FOODS

Summary Statements

14. Food is the most common cause of anaphylaxis in the outpatient setting and food allergens account for 30% of fatal cases of anaphylaxis. (D)
15. The most commonly implicated foods responsible for food-induced anaphylaxis include: peanuts, tree nuts, fish, shellfish, cow's milk, soy and egg. In addition sesame seed has recently been identified as a significant cause of food-induced anaphylaxis. (C)
16. Common themes associated with fatal food anaphylaxis include: reactions commonly involved peanuts and tree nuts; cutaneous and respiratory symptoms are frequently observed; victims are typically teenagers and young adults; patients have a prior history of food allergy and asthma; and there is a failure to promptly administer epinephrine. (C)

17. As is the case of anaphylaxis following other agents, asthma is a risk factor for more severe food-induced anaphylaxis. (C)
18. Biphasic anaphylactic reactions can occur in up to 25% of fatal and near-fatal food reactions. (C)
19. Serum tryptase measurements may not be elevated in cases of food-induced
20. The rapid use of injectible epinephrine has been shown to be effective in the initial management of food-induced anaphylaxis but subsequent doses may be needed. (C)
21. Patients who experience anaphylaxis should be observed for longer periods if they have experienced food-induced anaphylaxis. (C)
22. Food-dependant, exercise-induced anaphylaxis is a unique clinical syndrome in which anaphylaxis occurs within a few hours of specific food ingestion or any meal, and exercise. (C)
23. Patients with food allergy should pay close attention to food advisory labeling (e.g. "may contain"), which have become more prevalent. (C)

Foods are arguably the most common cause of anaphylaxis.^{94,95} The prevalence of food-induced anaphylaxis is increasing. The most frequently incriminated foods are peanuts, tree nuts, fish, and shellfish but other foods, such as sesame seeds, have become increasingly important as causes of food-induced anaphylaxis.^{95,96} Reactions can occur after the first known exposure.⁹⁷

Common themes have emerged regarding fatal reactions to foods. Most victims are teenagers or young adults who typically have a known food allergy. Asthma is a risk factor for mortality, and in many instances there has been failure to promptly administer epinephrine. Life-threatening reactions may present without any cutaneous manifestations, and can be characterized by only respiratory and/or cardiovascular symptoms.⁸⁸

Biphasic reactions appear to be more common in food-induced anaphylaxis than in anaphylaxis related to other causes, and have been reported in up to 25% of fatal or near fatal reactions.⁸⁸

Serum tryptase may be less frequently elevated distinguishing it from other causes. Serum tryptase may be less frequently elevated in cases of food-induced anaphylaxis than anaphylaxis produced by parenteral administration of allergen.⁹⁷

All patients with food-induced anaphylaxis should be prescribed autoinjectible epinephrine and instructed in its use. It has been well established that epinephrine is underutilized by individuals with food-induced anaphylactic events.⁹⁴ Although it is rare for patients with oral allergy syndrome to develop anaphylaxis, they may be at increased risk, based on reports of patients who have had anaphylactic reactions to foods after previously manifesting only the oral allergy syndrome.⁹⁸ Therefore, consideration could be given to prescribing such patients autoinjectible epinephrine.

At this time, there is no means for preventing food-induced anaphylaxis except for avoidance of those foods that are known or suspected of causing a reaction in a given patient.

Patients with food allergy should be instructed in how to properly interpret food labels and to avoid foods if the contents are not known.

Natural Rubber Latex (NRL)-Induced Anaphylaxis Summary Statements

24. There are three groups that are at high risk of reaction to latex: health care workers; children with spina bifida

and genitourinary abnormalities; and workers with occupational exposure to latex. (C)

25. ***In vitro* assays for IgE to NRL are typically recommended as a first step in evaluating latex sensitivity. However, due to their suboptimal diagnostic predictive value, positive and negative results must be interpreted based on the history. If the test is positive with a high clinical likelihood, latex sensitivity would be reasonable to pursue. In contrast, if the test is negative with a high clinical likelihood, latex sensitivity still must be considered. (C)**
26. **A standardized commercial skin test reagent for NRL is not available in the United States. In this regard, allergists have prepared NRL extracts from gloves to use for clinical testing. It should be noted, however, that such extracts prepared from gloves demonstrate tremendous variability in content of NRL allergen. Nevertheless, skin prick test with NRL extract to identify IgE-mediated sensitivity should be considered if patients are members of high risk groups or have a clinical likelihood of NRL allergy and have negative *in vitro* tests. (C)**
27. **Patients with spina bifida (regardless of a history of NRL allergy) and patients with a positive history of NRL allergy ideally should have all medical-surgical-dental procedures performed in a NRL safe environment. (D)**
28. **A NRL-safe environment is an environment in which no NRL gloves are used in the room or surgical suite and there is limited NRL accessories (catheters, adhesives, tourniquets, and anesthesia equipment or devices) which come in contact with the patient. (D)**
29. **In health care settings, general use of NRL gloves with negligible allergen content, powder-free NRL gloves, and nonlatex gloves and medical articles should be considered in an effort to minimize patient exposure to latex. Such an approach can diminish NRL sensitization of health care workers and patients and reduce the risk of reactions to NRL in previously sensitized individuals. (D)**
30. **Patients with a diagnosis of NRL allergy by history and/or skin testing can wear a medical identification bracelet, carry a medical identification card, or both. If patients have a history of anaphylaxis to NRL, it is important for them to carry auto-injectible epinephrine. (D)**

Latex sensitization is due to IgE-mediated reactivity to any number of antigens from *Hevea brasiliensis*, the source of latex. Sensitization occurs in up to 12 percent of health care workers, up to 75 percent of patients with spina bifida and in patients undergoing multiple surgical procedures.⁹⁹⁻¹⁰¹ Sporadic cases of latex induced anaphylaxis have been reported due to hair glue and plastic balls with latex pit.¹⁰² Atopic and latex-exposed individuals are also at higher risk. Individuals can be sensitized to minor or major antigens. At least 240 separate polypeptides can be discerned by two dimensional electrophoresis. Less than 25% of these have been shown to react with IgE from patients with latex allergy. They tend to cluster into groups of 11 proteins.¹⁰³ With exposure, sensitized individuals may develop urticaria, angioedema, allergic rhinitis, asthma and anaphylaxis. Latex-induced anaphylaxis from powdered latex gloves, as well as other sources, may present in the operating room in patients, surgeons, nurses or anesthesiologists (Table E5). Latex has been reported to account for up to 17% of intraoperative anaphylaxis.¹⁰³ The features of

intraoperative anaphylaxis may differ considerably from anaphylaxis not associated with surgical procedures. While cutaneous, hypotensive and respiratory events occur in both, hypotensive cardiovascular collapse is a feature of reactions to latex during surgery while dizziness or syncope is found largely in anaphylaxis induced by non-surgical procedures.¹⁰⁴ Latex-induced anaphylaxis is due to IgE-mediated mechanisms. Thus, in conjunction with a careful history and physical examination, detection of IgE to latex can be helpful in the diagnosis. Unfortunately, no standardized skin test reagent for latex is available in the United States, but “homemade” skin test preparations may be made from latex gloves. It is clear, however, that such “homemade” extracts are not standardized, and the amount of latex allergen within these extracts is highly variable. For diagnostic purposes, *in-vitro* tests for latex-specific IgE are available although the sensitivity of these tests may vary (see Allergy Diagnostic Testing; An Updated Practice Parameter). Due to the suboptimal diagnostic utility of these tests, results should be correlated with the clinical history. If the test is positive with a high clinical likelihood, latex sensitivity would be reasonable to presume. In contrast, if the test is negative with a high clinical likelihood, one cannot rule out latex sensitivity. *In vitro* tests have highly variable sensitivity and specificity characteristics. The sensitivity has been found to be as low as 50% and as high as 100%.^{104,105}

Latex-induced anaphylaxis may occur in a variety of situations, all involving direct contact with latex, usually gloves, or instruments, or with aerosolization of latex antigen adherent to the cornstarch powder of latex gloves. Thus, latex reactions can occur during operative procedures, when gloves are donned. Latex reactions may occur immediately with latex contact or may be delayed from 30 to 60 minutes. Intraoperative latex anaphylaxis may be related to the administration of drug through a latex port prior to surgery, or during the surgical procedure itself. Latex reactions have also been reported to occur during dental procedures from latex gloves or dams, during obstetrical or gynecologic examinations and during latex condom use. Spina bifida patients are potentially at risk during each surgical procedure because of the numbers of procedures they undergo.

Avoidance is extremely important. For the sensitized health care worker, latex gloves should not be worn and the worker’s colleagues should wear non-powdered latex gloves or non-latex gloves. The workplace should be “latex safe” with all non-glove latex devices replaced by non-latex devices. A “latex free” emergency cart (Table E6) should be available to treat reactions. Rubber stoppered vials should be avoided.

Settings in which latex avoidance precautions should be instituted in latex-sensitive patients might include surgical procedures, obstetrical or gynecologic examinations, or dental care. The surgical room, dental area or examination area should be free of latex devices and no latex gloves should be worn. Appropriate emergency medications should be available for treatment, should a reaction occur.

ANAPHYLAXIS DURING GENERAL ANESTHESIA, THE INTRA-OPERATIVE PERIOD, AND THE POST-OPERATIVE PERIOD

Summary Statements

31. **The incidence of anaphylaxis during anesthesia has been reported to range from 1 in 4000 to 1 in 25,000. Anaphylaxis during anesthesia can present as cardiovascular**

collapse, airway obstruction, and/or skin manifestations. C

32. It can be difficult to differentiate between immune and nonimmune mast cell-mediated reactions and pharmacologic effects from the variety of medications administered during general anesthesia. In addition, cutaneous manifestations of anaphylaxis are less likely to be apparent when anaphylaxis occurs in this setting. B
33. The evaluation of IgE-mediated reactions to medications used during anesthesia can include skin testing to a variety of anesthetic agents. B
34. The management of anaphylactic reactions that occur during general anesthesia is similar to the management of anaphylaxis in other situations. B
35. Thiopental allergy has been documented by skin tests. B
36. Neuromuscular blocking agents, such as succinylcholine, can cause nonimmunologic histamine release, but there have also been reports of IgE-mediated reactions in some patients. B
37. Reactions to opioid analgesics are usually caused by direct mast cell-mediator release rather than IgE-dependent mechanisms. B
38. Antibiotics that are administered perioperatively can cause immunologic or nonimmunologic reactions. B
39. Protamine can cause severe systemic reactions through IgE-mediated or nonimmunologic mechanisms. B
40. Blood transfusions can elicit a variety of systemic reactions, some of which might be IgE-mediated or mediated through other immunologic mechanisms. B
41. Methylmethacrylate (bone cement) has been associated with hypotension and various systemic reactions, although no IgE mechanism has been documented. C

Diagnosis. Diagnosis of anaphylaxis during general anesthesia and post-operatively is hampered by the following:

- The diagnosis of anaphylaxis depends in large part on the patient's ability to describe the event, and the patient cannot describe symptoms because they are unconscious or not fully conscious.
- Skin manifestations are an important and frequent indicator of anaphylaxis and skin manifestations may be masked by surgical drapes.
- Skin manifestations are less common than they are when anaphylaxis occurs in other settings.
- Cardiovascular collapse may be the sole manifestation of anaphylaxis and may be confused with other causes of cardiovascular collapse in this setting.
- Bradycardia occurs more often in this setting than in other settings of anaphylaxis and health care providers are more likely to think of anaphylaxis if the patient develops tachycardia.

The causes of anaphylaxis in this setting are varied, as are the mechanisms responsible for the reaction (Table E7). The most common cause of anaphylaxis during general anesthesia or post-operatively is neuromuscular blocking agents (muscle relaxants), which are responsible for sixty to seventy percent of episodes of anaphylaxis occurring during this period.¹⁰⁶⁻¹¹⁶

Most of the muscle relaxants cause direct release of mast cell histamine without the requirement for specific antibody. However,

life-threatening reactions usually are IgE-mediated.¹¹⁷ The tertiary or quaternary ammonium group, common to all muscle relaxants, is likely the immunodominant determinant recognized by IgE.¹¹⁸ The antigenicity of the shared ammonium structures may be responsible for cross-reactivity among the muscle relaxants. Cross-reactivity occurs most consistently between pancuronium and vecuronium.¹¹⁹ Cross-reactions also may occur between muscle relaxants and other classes of pharmaceuticals, based upon *in vitro* inhibition of specific-IgE binding to the muscle relaxants. Agents that potentially cross-react with muscle relaxants include: acetylcholine, choline, morphine, neostigmine, and pentolinium. Cross-inhibition suggests that previous exposure to these non-anesthetic drugs may sensitize individuals to muscle-relaxing agents, resulting in reactions among patients without prior anesthesia.¹²⁰ Three out of four cases of anaphylaxis to muscle relaxants occur in females, suggesting cross-reactivity with ammonium compounds in personal care products.¹²¹ Skin testing may be useful to determine the safest alternative for subsequent anesthesia following a suspected reaction, recognizing that nonimmunologic reactions are not identified by this diagnostic method.^{122,123} Skin testing is not recommended for preanesthetic screening of subjects without a history of suspected reactions.¹²⁴

Antibiotics frequently are administered before, during, or immediately after anesthesia and surgery. Allergic reactions to antibiotics, particularly anaphylaxis, may occur during the perioperative period. The antibiotics most commonly implicated in reactions during this period are β -lactam antibiotics and vancomycin.¹²⁵

Vancomycin is a glycopeptide antibiotic selectively used for treatment of resistant organisms and for use in individuals with penicillin allergy. Administration, especially when it is rapid, may result in life-threatening, non-IgE-mediated anaphylaxis.¹²⁶⁻¹²⁸ Direct histamine release and direct myocardial depression partially explain this phenomenon.¹²⁹ These nonimmunologic reactions to vancomycin can be reduced or eliminated by administering this drug as a dilute solution, dissolved in at least 200 mL, and infused over at least a 2 hour period. IgE-mediated anaphylaxis to vancomycin is much less common. Skin testing with a concentration of 0.15 mg/mL or less has been reported, but the reliability of this testing is less than with penicillin skin testing.^{130,131} Nevertheless, skin testing with vancomycin may have some value in distinguishing rate-related adverse events from anaphylaxis.

Dextran and hydroxyethyl starch (HES), large-molecular-weight polysaccharides, may be used as a non-blood, high-oncotic fluid replacement during surgery. These agents are infrequently associated with adverse reactions and anaphylaxis. Estimates of reaction rates are 0.008% to 0.08% for dextran and 0.08% for HES.¹³² Specific antibodies can be detected to dextran or HES, but their clinical significance is unknown.^{133,134} Confirmation of dextran or HES as the cause of an adverse reaction is limited by the absence of validated serologic or skin tests. Skin-test reactivity to undiluted solutions has been described but is of unknown predictive value.¹²¹ Case reports also describe systemic reactions to albumin, but the mechanism for such adverse effects is not known.¹¹⁹

Intravenous drugs used for anesthetic induction can cause perioperative anaphylaxis. More than 290 cases of anaphylaxis are reported in the literature from the use of *barbiturates*, especially thiopental. However, the reaction rate with barbiturates is only 1:25,000, with the reported occurrence of reactions reflecting

the common use of these compounds.¹¹⁷ Women are three times more likely to have reactions from thiopental than men.^{121,124} Most of the adverse reactions with barbiturates, particularly thiopental, are caused by specific-IgE antibody, although direct histamine-releasing activity also occurs.^{121,135-137} The importance of immunologic cross-reactivity is unknown. Skin testing may be clinically useful, but the concentration of drug testing must be less than the concentration that result in irritation. See Table E8 for the concentration of anesthetic agents that has been recommended for intradermal skin testing.^{122,123}

Propofol is a nonbarbiturate induction agent that is potentially useful if sensitivity to barbiturates is a concern.¹³⁸ IgE-mediated reactions from propofol may occur^{139,140}, however, most adverse reactions to propofol are non-immunologic.¹⁴² Propofol may directly stimulate histamine release, and this effect may be greater when administered with muscle relaxants.¹⁴²

Narcotics used in peri-operative period are a common cause of flushing and urticaria following intravenous administration. Anaphylaxis, in contrast, is very rare.^{143,144} Dermal mast cells express opioid receptors that bind to the narcotic and stimulate histamine release. Other populations of mast cells do not express this receptor. Cutaneous flushing and hives often occur after intravenous morphine administration, but with rare exceptions, the amount of histamine release does not result in hypotension or bronchospasm.¹⁴⁵ Reducing the rate of opioid administration usually limits the severity of these reactions. *Fentanyl* does not directly stimulate histamine release by way of the mast-cell opioid receptor.¹⁴⁵ There are reports of anaphylaxis to morphine and fentanyl.¹⁴⁶ The predictive value of skin testing with morphine has not been determined.

Intravenous *protamine*, an agent used to reverse heparin anticoagulation, may cause both anaphylactic and anaphylactoid reactions; the latter is characterized by increases in pulmonary blood pressure. Potential pathophysiologic mechanisms are numerous and varied.¹⁴⁷⁻¹⁵¹ A case control study (multivariate odds ratio [95% confidence interval]) showed that previous neutral protamine Hagedorn insulin use (8.18 [2.08, 32.2]), fish allergy (24.5 [1.24, 482.3]), and other medication allergy (2.97 [1.25, 7.07]) are independent risk factors for anaphylaxis¹⁵⁰. The authors estimate that up to 39% of cardiopulmonary bypass patients have one or more of these risk factors. Allergy to fish has not been conclusively shown to be associated with protamine allergy.^{155,156} Skin prick tests and specific IgE antibodies have not been demonstrated to be clinically useful in the diagnosis of hypersensitivity to protamine.

Although *benzodiazepines* are frequently used peri-operatively, adverse reactions are exceedingly rare. The mechanism of clinical adverse reactions has not been studied. Specific IgE has not been detected by skin tests or in-vitro tests.^{157,158}

Local anesthetic agents readily induce cell-mediated immunologic reactions when applied topically to the skin, but humoral immune responses are rare. Adverse effects from local anesthetics are not uncommon, but immunologically mediated reactions following parenteral administration are very unusual. Percutaneous testing, followed by intracutaneous testing, usually is performed with one or more local anesthetics. Dilutions of the anesthetics may be considered for the initial testing if the history is highly suggestive of anaphylaxis. Ideally anesthetic agents with and without preservatives are used to determine if preservative sensitivity, rather than anesthetic allergy, could be responsible for the reaction. Local anesthetics without epinephrine are preferable if the history is suggestive of an anxiety response.

The *management* of anaphylaxis in the peri-operative period is similar to the management of anaphylaxis in other situations. Reports that arginine vasopressin may be superior to epinephrine require confirmation before any change in treatment recommendations.¹⁵⁹

The *diagnosis* of perioperative anaphylaxis is challenging because of the multiple drugs administered, concurrently or sequentially, and the effects of anesthesia itself. An elevated serum tryptase level 1 to 6 hours after suspected anaphylaxis suggests mast cell degranulation and supports the diagnosis of anaphylaxis in the presence of a typical history and clinical findings.^{22,25,160} Additional diagnostic testing for the agent responsible for mast cell degranulation, usually by measuring specific-IgE, would be advisable if the serum tryptase were elevated. A normal tryptase level, however, does not exclude anaphylaxis.

Testing for specific-IgE to a suspected, causal agent is not recommended until several weeks after a reaction, because transient decreases in measurable allergen specific-IgE may occur after anaphylaxis. Skin tests with agents used during the peri-operative period may be difficult to interpret because many drugs can cause direct mast-cell histamine release in the absence of specific-IgE. Nonetheless, skin testing has been shown to be valuable in evaluating anaphylaxis to barbiturates, streptokinase, penicillin, insulin, local anesthetic, and latex. *In vitro* testing for specific IgE antibodies has been reported for muscle relaxants, thiopental, morphine, propofol, and latex.

The *prevention* of peri-operative anaphylaxis is an elusive ideal because of the rare occurrence of reactions, multiple pathophysiologic mechanisms (many of which are undefined), the limited ability to test for sensitization and the limited ability to define the risk of recurrence. A careful medical history that focuses on previous adverse reactions is most important. A prior medication reaction nonspecifically increases the possibility of adverse reactions, and multiple previous medication reactions pose a greater risk. Atopic individuals may be at increased risk because of either an increased frequency of reactions or, more often, an increased severity of reactions. Previous anesthetic-associated reactions should be evaluated thoroughly, with specific testing if indicated. IgA-deficient subjects should receive washed red blood cells and not whole blood to avoid exposure to exogenous IgA. Intraoperative antibiotics should be administered slowly with careful hemodynamic monitoring. Drugs with histamine-releasing properties (e.g., morphine, d-tubocurarine, vancomycin, quaternary muscle relaxants) should be administered as slowly as possible, particularly in subjects with asthma or cardiopulmonary disease. Pretreatment regimens, as used for patients who have experienced anaphylactoid reactions to radiocontrast material, have not been proven to prevent reactions, but may reduce the severity of such reactions even if a non-IgE mediated mechanism is suspected.

Peri-operative anaphylaxis, mediated by immunologic, non-immunologic, or undefined mechanisms, is becoming more common, probably because of more frequent use of anesthesia and the increasing complexity of utilized drugs. Recognition and immediate treatment are particularly important because anesthetized patients are at greater risk for adverse outcomes caused by the physiologic effects of anesthesia. Vigilance for the signs of anaphylaxis and consideration of risk factors, with possible modification of the agents used, will likely reduce the morbidity and mortality associated with these reactions.

SEMINAL FLUID ANAPHYLAXIS

Summary Statements

42. Coital anaphylaxis caused by human seminal fluid has been shown to be due to IgE-mediated sensitization to seminal plasma proteins of varying molecular weight. C
43. Post-coital local reactions to human seminal plasma are probably IgE-mediated based on successful response to rapid seminal plasma desensitization. C
44. History of atopic disease is the most consistent risk factor for seminal fluid-induced anaphylaxis. C
45. The diagnosis of seminal plasma anaphylaxis may 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 via seminal plasma. D
46. Greater than 90% of the allergenic proteins range between 12 to 75 kd. Prostate specific antigen has been demonstrated to be a relevant allergen in some cases. C
47. 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. C
48. Subcutaneous immunotherapy to properly prepared fractions of seminal plasma collected from male partners has been successful in preventing anaphylaxis to seminal plasma. C
49. Successful intravaginal graded challenge with whole seminal plasma of the male partner has been reported in a few cases but the duration of protection is unknown. This treatment approach may be considered prior to pursuing desensitization using relevant seminal plasma protein fractions. C
50. Patients with seminal plasma allergy may be able to conceive without undergoing desensitization, by artificial insemination with washed spermatozoa. C

Anaphylaxis due to coital exposure to human seminal fluid is a rare occurrence. Since the initial report in 1958,¹⁶¹ approximately 30 cases of seminal fluid induced anaphylaxis have been described.¹⁶²⁻¹⁶⁴ 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 12-75 kD.¹⁶⁵⁻¹⁶⁷ In rare cases, spermatozoa have been identified as the source of allergens inducing a cell-mediated reaction.¹⁶⁸ Coital anaphylaxis has also been attributed to exogenous allergens transferred via semen during sexual intercourse. Such unusual reactions occur when a male partner ingests a food (e.g., walnuts) or drug (e.g., penicillin) to which there is established sensitization in the female partner.¹⁶⁹

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, transfer of food or drug proteins from the male sexual partner to the female who may 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.¹⁷⁰ Failure of condoms to prevent anaphylaxis suggests either incorrect condom technique or concurrent sensitization to latex.¹⁷¹ Localized vulvar and vaginal burning may occur as isolated symptoms or in conjunction with itching and swelling following ejaculation.¹⁷² There is no evidence that localized vaginal seminal plasma hypersensitivity increases the likelihood of a future systemic reactions.

The most significant risk factor for seminal plasma protein anaphylaxis is a history of allergic asthma or atopic dermatitis.^{163, 167, 173} Anecdotal case reports of seminal fluid anaphylaxis have occurred post-partum, after gynecologic surgery and following injection of anti-Rh immune globulin.¹⁶³ It has not been established if such events are coincidental or could somehow modulate immune tolerance resulting in sensitization to seminal fluid proteins. Reactions have also been observed in women whose male partners have recently undergone prostatectomy or vasectomy.¹⁷⁴ Anaphylactic events have been reported in women with multiple previous sexual encounters or in others, after the first coital act.¹⁶³ Post-coital allergic reactions are not specific to one 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 less than two sexual partners.¹⁶³

The diagnosis must be confirmed by *in vivo* and/or *in vitro* demonstration of sensitization to seminal fluid proteins.¹⁶⁵ Based on available data, *in vitro* tests (e.g., RAST, ELISA) of serum specific IgE appear to be less sensitive than skin testing.¹⁶³ A negative serologic test 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. Prior to skin testing, the male donor must be screened for viral hepatitis, syphilis and HIV infection and if there is evidence of infection, skin testing should not be performed.^{165, 167, 168}

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 tests to the same fractions is highly predictive of a successful treatment outcome with seminal plasma protein desensitization.¹⁷⁵

Consideration must be given to the psychologic impact of this condition on the patient, his/her 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.¹⁷⁴ Once the diagnosis is suspected, the patient must be advised to avoid coital exposure to seminal fluid. This can be achieved by either temporary cessation of intercourse or with the correct use of latex 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, the male partner should avoid the causative food or drug prior to engaging in sexual intercourse.^{168, 169} It is essential that patients and their partners be trained in the emergency use of autoinjectable

epinephrine. 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 severe anaphylaxis.¹⁷⁵

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 only be performed in specialized centers and under the supervision of experienced physicians.^{165-168,170,176}

Successful intravaginal graded challenges have been reported in women diagnosed with human seminal plasma anaphylaxis confirmed by skin prick test reactivity to whole seminal plasma.¹⁷⁷⁻¹⁸² As with parenteral desensitization protocols, frequent intercourse (two to three times per week) is required to maintain the desensitized state. The efficacy of intravaginal graded challenge is based entirely on anecdotal reports. Moreover, the duration of the protective effect is unknown. Graded intravaginal challenges have been less effective in women with localized seminal plasma hypersensitivity reactions.¹⁸³

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 get pregnant as it has not been associated with infertility.^{181,183}

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

- Barrier condoms can be successful tools of management. In the latex-allergic patient, polyurethane condoms can be used.
- In cases due to the transfer of exogenous allergens, the male partner should avoid the food or drug in question.
- The patient and spouse should be supplied with and trained in the use of an automatic epinephrine injector.
- When these therapies are not effective or are unacceptable, immunotherapy can be instituted. Couples should be informed that successful pregnancies have occurred in patients with this problem. There is no association between seminal fluid hypersensitivity and infertility.

EXERCISE-INDUCED ANAPHYLAXIS

Summary Statements

- 51. Exercise is the immediate trigger for the development of symptoms in exercise induced anaphylaxis (EIA). Typical symptoms include extreme fatigue, warmth, flushing, pruritus, and urticaria, occasionally progressing to angioedema, wheezing, upper airway obstruction, and collapse. A**
- 52. The pathophysiologic events during exercise that precipitate symptoms are not known, although promising lines of research exist. C**
- 53. Some patients experience symptoms only if other contributing factors or “co-triggers” are present in association with exercise. These co-triggers include ingestion of specific foods, or in some patients ingestion of any food, non-steroidal antiinflammatory drugs, and high pollen levels. C**
- 54. The clinical history should focus on identification of these possible co-triggers. Evaluation for sensitization to food allergens, particularly grains and seafood,**

should be performed. The diagnosis is usually made based upon history and exclusion of other disorders. Exercise challenge testing does not consistently reproduce symptoms. C

- 55. All patients with exercise-induced anaphylaxis must be advised to stop exercising immediately at the first sign of symptoms because continued exertion causes the attacks to worsen. In addition, all patients should carry epinephrine auto injectors and exercise with a partner who can recognize symptoms and administer epinephrine if necessary. D**
- 56. Prophylactic medications are not effective for preventing attacks in the majority of patients, although a small subset does appear to benefit from daily administration of H1 antihistamines. D**
- 57. The prognosis of patients with exercise-induced anaphylaxis is generally favorable, although at least one fatality has been reported. Most patients experience fewer and less severe attacks over time. It is unclear if this is the result of trigger avoidance or a change in the underlying condition. C**

Exercise-induced anaphylaxis (EIA) is characterized by symptoms of mast cell mediator release in the setting of physical exertion. Typical early signs and symptoms begin a few minutes into exercise, and include diffuse warmth, flushing, pruritus, urticaria, and fatigue.^{184,185} If exercise continues, there may be progression to angioedema of the face and extremities, gastrointestinal symptoms, laryngeal edema, hypotension, or collapse. Wheezing can occur, although it is less common than other symptoms. Some patients experience disabling headache that persists for several days after an episode.¹⁸⁵ Attacks occur sporadically and unpredictably, even though most patients with this disorder exercise regularly.

Vigorous exercises, such as jogging, racquet sports, dancing, and aerobics, are most often implicated, although lower levels of exertion, such as brisk walking or yard work, are capable of triggering attacks in some patients.¹⁸⁶ Cessation of exercise usually results in improvement or resolution of symptoms, although, patients often do not instinctively stop exercising when they first experience symptoms. Instead, many try to run for help or sprint home, and this precipitates a dramatic worsening of symptoms. Once the patient either stops exercise or receives treatment, symptoms may dissipate rapidly or last for several hours. It is not known how often this disorder results in fatal anaphylaxis, although at least one death has been reported.¹⁸⁷ Such events are likely underdiagnosed and misdiagnosed, as with other causes of fatal anaphylaxis.

Many patients require the presence of one or more other factors in order to develop symptoms upon exercise. Reported “co-triggers” include the ingestion of specific foods,¹⁸⁸ the ingestion of any solid food, non-steroidal anti-inflammatory drugs (NSAIDs),^{186,189} alcoholic beverages, menstruation,⁶ or, seasonal pollen exposure in pollen-sensitized patients.¹⁸⁶ Typically, each trigger is tolerated if there is no association with the other trigger, e.g., 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 most cases, exposure to the co-trigger occurs first, followed by exercise, with the latter triggering symptoms. Ingestion of NSAIDs may precede exercise by hours to a day, whereas food or alcohol ingestion typically has occurred within 4 to 6 hours before

exercise. The foods most commonly implicated are wheat, other grains, nuts, and seafood, although a wide variety of foods have been reported.^{188,190}

EIAN is a rare disorder. One study estimated the prevalence of EIAN among Japanese adolescents to be approximately 0.03 percent, with no clear gender preference.¹⁹¹ The prevalence of patients with purely exercise-triggered anaphylaxis, relative to those who require exercise plus one or more cofactors, is not known, although food-dependent anaphylaxis has been reported more often.¹⁹²

The pathophysiology of EIAN is not well-understood, although there is evidence that it is a mast cell-mediated disorder. Skin biopsies demonstrating degranulation of dermal mast cells following attacks,¹⁹³ and transient elevations in plasma histamine^{194,195} and serum tryptase¹⁹⁶ have been documented in case reports. However, the precise trigger(s) for mast cell activation have not been conclusively identified, and the events during exercise that may alter the activity of mast cells or other leukocytes have not been defined.

The diagnosis of exercise-induced anaphylaxis is based upon a meticulous clinical history, skin or *in vitro* testing for IgE-mediated allergy, and occasionally, documenting mast cell activation if this can be determined in the minutes or hours following an attack.

As part of the history, each episode that can be recounted by the patient should be reviewed in detail, to discern if any co-triggers were present. A careful skin examination for lesions of urticaria pigmentosa and a baseline serum tryptase level can be performed to evaluate for mastocytosis, which can present with anaphylaxis upon exertion.

Skin testing for sensitization to foods and environmental allergens helps to define each patient's potential co-triggers. In food dependent -EIAN, IgE-mediated allergy to precipitating foods is usually, although not always demonstrable. Patients who do not initially test positive to foods that appear by history to be co-triggers, may over time develop positive skin tests to suspected food. Thus, if the history suggests a food co-trigger but testing is negative, repeat testing over time may be useful.

The diagnosis of EIAN can be confirmed by eliciting symptoms with treadmill testing. However, symptoms are difficult to reproduce.^{192,197} The differential diagnosis includes arrhythmias and other cardiovascular events, but such events do not include pruritus, urticaria, angioedema, or upper airway obstruction. Exercise-induced bronchoconstriction presents with symptoms that are limited to the airways. Exercise-associated gastroesophageal reflux could mimic mild symptoms of EIAN, although, urticaria and/or pruritus are not observed.

Cholinergic urticaria, a physical urticaria usually limited to the skin, can mimic the early cutaneous symptoms of EIAN. Cholinergic urticaria is characterized by initially punctate (1 to 3 mm in diameter) wheals with surrounding erythema of the affected skin. Cholinergic urticaria is elicited by raising the core body temperature, such as with a sauna or hot bath, very strong emotion, or very spicy food and can be discerned with a careful history and confirmed with passive warming. A minority of patients with EIAN develop punctate urticaria,¹⁹⁸ although most have larger wheals (10 to 15 mm in diameter). Patients with punctate urticaria who develop symptoms in extracutaneous organs should be considered to have EIAN. Exercise is necessary to elicit the symptoms of EIAN; passively raising the core body temperature should not elicit symptoms in such patients.¹⁹⁹

The management of EIAN must be individualized, depending upon the severity of symptoms, the presence of co-triggers, and the patient's desire to continue exercise. The patient must carry or have immediate access to autoinjectible epinephrine whenever they exercise. Patients with EIAN should exercise with a partner or in a supervised setting at all times. The companion should be educated about the condition and be capable of administering epinephrine. Patients must be vigilant for early signs of EIAN (e.g., flushing, pruritus) and stop exercise immediately if these develop. It is imperative that patients understand the importance of immediately stopping exercise at the first sign of symptoms. For patients with identifiable co-triggers, avoidance of these factors may allow them to resume exercise safely. For example, patients who demonstrate sensitization to a food should avoid that food completely if it is not an integral part of the diet. Foods that are essential to the diet should not be eaten during the 6 hours prior to exercise.

Pharmacologic therapy cannot be relied upon to prevent EIAN. Oral H1 antihistamines, corticosteroids, oral cromolyn sodium,²⁰⁰ H2 antihistamines, or omalizumab, have not been evaluated in controlled studies, and/or have not been shown to be consistently effective. H2 antihistamines, specifically in patients with food dependent -EIAN, should be avoided because there is preliminary evidence that H2 antihistamines may interfere with normal digestion of food allergens and therefore could augment a reaction.²⁰¹⁻²⁰³

Most patients with EIAN report fewer attacks over time. Much of this improvement may be attributable to modifications in exercise habits and recognition of co-triggers. A questionnaire administered to 279 patients, with EIAN 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. Patients reported avoiding exercise during extremely hot, cold, or humid weather conditions, during pollen season (pollen-allergic patients), after eating, and after taking NSAIDs.¹⁸⁶ Thus, with proper counseling and careful self-monitoring, most patients are able to continue exercise and suffer fewer attacks over time.

IDIOPATHIC ANAPHYLAXIS

Summary Statements

- 58. The symptoms of idiopathic anaphylaxis are identical to those of episodes related to known causes. C**
- 59. Patients with idiopathic anaphylaxis should receive an intensive evaluation, including a meticulous history to rule out a definite cause of the events. C**
- 60. There might be a need for specific laboratory studies to exclude systemic disorders, such as indolent systemic mastocytosis. This might include a measurement of serum tryptase when the patient is asymptomatic, measurement of total tryptase during or within 4 hours of an acute episode, and the ratio of mature (β) tryptase to total tryptase during an episode. To exclude hereditary angioedema or acquired C1 inhibitor deficiency, a C4 concentration can be obtained as it will be reduced during or in the absence of severe angioedema in those conditions but normal in idiopathic anaphylaxis. C**
- 61. There might be a need for selective skin testing for detection of anti-food IgE antibodies when foods have been ingested within 2 hours of the onset of an episode. C**

62 Empiric use of oral corticosteroids combined with H₁ antagonists has been demonstrated to reduce the frequency/severity of episodes. C

63 Patients with idiopathic anaphylaxis should carry epinephrine, know the indications for self-administration, and can carry information denoting their condition. C

The pathogenesis of idiopathic anaphylaxis is not understood. Evidence of mast cell activation in idiopathic anaphylaxis includes elevated urinary histamine,^{204,205} serum tryptase,^{206,207} and mature (β) tryptase.²⁰⁰ Skin biopsies from patients with idiopathic anaphylaxis reveal increased numbers of mast cells compared to normal individuals but considerably less than in non-lesional or lesional skin from patients with either urticaria pigmentosa or indolent systemic mastocytosis.²⁰⁸ Lymphocyte activation has been identified in blood samples obtained up to 24 hours after an episode, demonstrated by increases in CD3+HLA DR+ T cells and in activated CD19+CD23+ B cells.²⁰⁹ Idiopathic anaphylaxis is a corticosteroid-responsive condition based on empiric treatment with prednisone.^{7,210}

The diagnosis of idiopathic anaphylaxis must be considered in those cases of anaphylaxis for which neither a causative allergen (e.g., medication, food, sting), inciting physical factor, or disease state can be identified. Episodes occur primarily in adults or adolescents with infrequent episodes in children. Almost one-half of patients with idiopathic anaphylaxis have been found to be atopic. They may also experience anaphylaxis from recognized causes such as exercise, medication, or food.^{7,9}

The diagnosis of idiopathic anaphylaxis remains one of exclusion. Patients with idiopathic anaphylaxis should receive careful evaluation for possible causes, with emphasis on the history of events in the 3 hours prior to an episode. Selective skin testing with foods (and if indicated to fresh food extracts) may be of value. Indolent systemic mastocytosis must be excluded. Consistently elevated serum tryptase levels suggest the presence of indolent systemic mastocytosis since the serum tryptase (total and α tryptase) will be elevated in the absence of episodes of anaphylaxis. In contrast, serum tryptase levels will be normal in quiescent idiopathic anaphylaxis. A bone marrow examination may be indicated in patients with a diagnosis of idiopathic anaphylaxis even in the absence or elevated tryptase levels if salmon colored, hyperpigmented macules and papules consistent with urticaria pigmentosa are found.^{211,212} The differential diagnosis of idiopathic anaphylaxis includes hereditary angioedema or acquired C1 inhibitor deficiency. Some patients with idiopathic anaphylaxis present with massive enlargement of the tongue and/or life-threatening upper airway obstruction due to pharyngeal or laryngeal angioedema, but their C4 concentration is not reduced.

The acute treatment of idiopathic anaphylaxis is the same as the treatment for other forms of anaphylaxis. Prophylactic treatment with oral prednisone at 60-100 mg daily in combination with H₁ antagonists for 1-2 weeks followed by decreasing alternate day prednisone over 3 months has resulted in reduced severity and frequency of anaphylaxis. Such empiric treatment has been used for patients with 6 or more episodes/year or 2 episodes in 2 months of idiopathic anaphylaxis.^{7,210} Patients should carry auto-injectible epinephrine and be instructed in its use. Patients should also carry identifying information such as by Medic Alert.

If a patient does not respond to prophylaxis for idiopathic anaphylaxis, it is necessary to re-consider the diagnosis at each visit. Patients who experience a greater number of episodes when

receiving daily or alternate day oral corticosteroids could in fact have factitious anaphylaxis, globus hystericus, laryngopharyngeal reflux or undifferentiated somatoform idiopathic anaphylaxis.^{212,213} The symptoms of idiopathic anaphylaxis are identical to those of episodes related to known causes.

ANAPHYLAXIS TO ALLERGEN IMMUNOTHERAPY EXTRACT (VACCINE)

Summary Statements

- 64. There is a small risk of near-fatal and fatal anaphylactic reactions to allergen immunotherapy. C**
- 65. Patients with asthma, particularly if poorly controlled, are at higher risk for serious potentially life-threatening anaphylaxis to allergen immunotherapy injections. C**
- 66. It is unclear whether patients taking beta adrenergic blocking agents are at increased risk of having a serious systemic reaction to allergen immunotherapy injections. B**
- 67. Anaphylaxis in patients taking beta adrenergic blocking agents may be more difficult to treat. C**
- 68. Allergen immunotherapy vaccines should be administered only by health care professionals trained in the recognition and treatment of anaphylaxis, only in health care facilities with the proper equipment for the treatment of anaphylaxis, and in clinics with policies and procedures that minimize the risk of anaphylaxis. D**

Based on surveys from 1945 to 2001, the rate of all systemic reactions to subcutaneous allergen immunotherapy (AIT) injections has been estimated at 0.25-1.3%.^{214,215} Fatal anaphylaxis to AIT injections occurs at an estimated rate of 1 in 2.5 million injections²¹⁶⁻²¹⁹ and near-fatal anaphylactic reactions at a rate of 1 in every 1 million injections.²²⁰ Thus, although anaphylactic reactions to AIT are uncommon, physicians and patients should be prepared for possible systemic reactions.

Numerous studies suggest that patients with asthma, particularly poorly controlled asthma, are at higher risk for serious systemic reactions to AIT injections.^{216,218,219,221, 222} The few patients who died from anaphylaxis after AIT injections were more likely than patients surviving anaphylaxis to have previously required hospitalization for acute asthma.^{220,223} It is reasonable, therefore, to assess asthma symptoms and measure peak expiratory flow rate before administering allergen injections to patients with poorly controlled asthma. In addition, it is important to remember that a subset of asthmatics may poorly perceive their level of control. Uncontrolled asthma must be stabilized before AIT injections are administered.²²²

Although studies have reported that patients receiving AIT with aeroallergens or Hymenoptera venom who are taking β -adrenergic blocking agents are at no greater risk of systemic reactions than AIT treated patients not taking β -blockers, there is still concern that these studies contain substantial bias and other methodologic flaws.^{64,224} Certainly however, β -adrenergic blockers may inhibit the beneficial therapeutic effects of epinephrine during anaphylaxis and enhance the need for subsequent treatment in the hospital.^{225,226} Therefore, a cautious attitude should be adopted toward the concomitant use of β -adrenergic blockers and inhalant AIT.²²² In patients with life-threatening stinging insect hypersensitivity, the benefits of venom immunotherapy may outweigh any risk associated with concomitant β -adrenergic blocker administration.²²²

Although previous studies had suggested that local reactions were not predictive of systemic reactions, a recent retrospective study reported that patients who have systemic reactions had an approximately 3-fold greater frequency of preceding large local reactions.²¹⁸ This study indicated that patients with *repeated* large local reactions may be at increased risk for AIT-induced anaphylaxis. However, this issue remains controversial.²²⁷

AIT injections should be administered by health care professionals trained in the recognition and treatment of anaphylaxis. AIT should be administered only in health care facilities with proper equipment for the treatment of anaphylaxis including epinephrine, oxygen, oral airway, and equipment for the administration of intravenous fluids and medications.²²² AIT should be administered in a setting with policies and procedures that minimize the risk of anaphylaxis. These policies and procedures should reduce the risk of dosing errors, ensure proper training of personnel, and facilitate treatment of anaphylaxis.²²² Most systemic reactions occur within 30 minutes after an AIT injection,²²⁰ although late reactions do occur.^{214,228} To better recognize and treat anaphylactic reactions, patients should wait after receiving an AIT injection for 30 minutes at the location of the AIT injection.²²² In addition, patients at increased risk of systemic reactions, particularly if they have a history of reactions beginning longer than 30 minutes after an injection, might need to be provided with autoinjectable epinephrine, and instructed in its use.^{214,222} Some patients may need to remain at the location where the AIT injection was given for more than 30 minutes after an injection.

ANAPHYLAXIS TO DRUGS AND BIOLOGICAL AGENTS

Summary Statements

- 69. Low-molecular-weight medications induce an IgE-mediated reaction only after combining with a carrier protein to produce a complete multivalent antigen. B**
- 70. Penicillin is the most common cause of drug-induced anaphylaxis. C**
- 71. Penicillin spontaneously degrades to major and minor antigenic determinants, both of which should be included in skin testing for penicillin hypersensitivity. B**
- 72. The negative predictive value of penicillin skin testing with both major and minor determinants (for immediate-type reactions) is between 97% and 99% (depending on the reagents used), and the positive predictive value is at least 50%. B**
- 73. The degree of cross-reactivity between penicillin and cephalosporins appears to be low. C**
- 74. The degree of cross-reactivity between penicillin and cephalosporins or carbapenems appears to be low. C**
- 75. Patients with a history of penicillin allergy who have negative penicillin skin test responses can safely receive cephalosporins. B**
- 76. Patients who need to receive cephalosporins and who have a history of penicillin allergy and positive penicillin skin test responses can (1) receive an alternate (non-beta lactam) antibiotic; (2) receive a cephalosporin through graded challenge; or (3) receive a cephalosporin through rapid desensitization. C**
- 77. Aztreonam does not cross-react with other beta lactams, except ceftazidime, with which it shares a common R-group side chain. B**

- 78. Diagnosis of IgE-mediated reactions to non-beta lactam antibiotics is limited by a lack of knowledge of the relevant allergenic determinants and/or metabolites. C**
- 79. Aspirin and nonsteroidal anti-inflammatory drugs are the second most common cause of drug-induced anaphylaxis. C**
- 80. Anaphylactic reactions to aspirin and other nonsteroidal anti-inflammatory drugs appear to be medication specific. D**
- 81. Anaphylactic reactions to omalizumab have occurred, and post-marketing data indicate that there is an incidence of approximately 0.2% in treated patients. These reactions have been unusual in that they can be delayed in onset and progressive. C**
- 82. Based on the fact that anaphylactic reactions to omalizumab can be delayed, an observation period of two hours for the first three injections, and 30 minutes thereafter for subsequent injections is indicated. D**
- 83. All patients receiving omalizumab should be prescribed an automatic epinephrine injector and instructed in its use. The physician should ensure that the patient has such an injector with them, at the time of the visits to the office for injection. D**
- 84. A pre-assessment (before the injection of omalizumab) of the patient's current health status should be made. This should include vital signs, an assessment of asthma control, and measurement of lung function. D**

Medications are the second most common overall cause of anaphylaxis, and the primary cause of anaphylaxis in adults. The most common classes of drugs producing anaphylaxis are: 1) antibiotics, especially β -lactam antibiotics, and 2) nonsteroidal antiinflammatory drugs.

Unfortunately there are not adequate skin tests for demonstrating IgE-mediated (allergic/anaphylactic) potential to most drugs. Therefore, in most instances, the diagnosis of drug hypersensitivity is based on history and/or challenge.

BETA LACTAM ANTIBIOTICS

If the patient is skin tested with the penicillin product itself, a minor determinate mixture, and the major determinant (penicilloyl polylysine), there is a positive predictive value of 50% or greater.^{219, 229} Patients with a positive penicillin skin test response should receive an alternative antibiotic or undergo desensitization if penicillin is mandated. Skin testing with penicillin G and penicilloyl-polylysine, has a negative predictive value of 97% which increases to 99% if a minor determinant mixture is used.²²⁹⁻²³¹ Patients with negative skin tests to the major and minor determinants of penicillin can be safely treated with penicillin. Penicillin skin testing might sensitize a very small proportion of patients.²³²

Penicillin and cephalosporins share a common beta lactam ring, but the extent of allergic cross-reactivity between the two families appears to be relatively low. Some studies have demonstrated no serious allergic reactions in large groups of patients with a history of penicillin allergy who were treated with cephalosporins.²³³⁻²³⁵ However, patients in these retrospective studies were diagnosed with penicillin allergy on the basis of the history alone and, history is known to be poor predictor of true penicillin allergy. About 90% of patients with a history of penicillin allergy are able to receive penicillin without reaction.^{219, 230} Only a small percentage of patients with a history

of penicillin allergy and a positive penicillin skin test experience an allergic reaction on being challenged with cephalosporins²³⁶. Nevertheless, fatalities have occurred when patients with a history of penicillin allergy are not skin tested for penicillin and given cephalosporins.²³⁷ There are also case reports from the 1970s of cephalosporin-induced anaphylactic reactions in patients with a history of penicillin allergy,^{238,239} but these patients did not undergo penicillin skin testing, and early cephalosporins were known to contain trace amounts of penicillin.

Patients with a history of penicillin allergy who have negative penicillin skin tests are at no higher risk of experiencing allergic reactions when given cephalosporins than the general population²³⁹. If the patient has a history of penicillin allergy and a positive penicillin skin test, and needs to receive cephalosporin, the physician has three options: (1) administration of an alternate non-β lactam antibiotic; (2) administration of a cephalosporin through graded challenge; or (3) desensitization to the cephalosporin.²³⁹

Aztreonam (Monobactam) does not-cross react with penicillin or other β-lactams, aside from ceftazidime, with which it shares an identical R-group side chain.²⁴⁰ Therefore patients allergic to penicillin and other β-lactams (except for ceftazidime) can usually safely receive aztreonam. Similarly, patients allergic to aztreonam can safely receive other β-lactams, except for ceftazidime.

The extent of clinical cross-reactivity between carbapenems and other β-lactams appears to be very low, despite an initial report to the contrary.⁸³ Among penicillin skin test-positive patients, 111/112 were skin test-negative to imipenem and all 111 tolerated challenge with imipenem.²⁴¹ Similar tolerability was seen with meropenem in this same group of individuals.²⁴² Penicillin skin test-negative patients may safely receive carbapenems. Penicillin skin test-positive patients and patients with a history of penicillin allergy who do not undergo skin testing should receive carbapenems via graded challenge.

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, a positive result suggests the presence of drug-specific IgE antibodies.²⁴³

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), including COX-2-specific inhibitors, have been reported to produce anaphylactic reactions. Aspirin and NSAIDs are the second most common cause of drug-induced anaphylaxis (after antibiotics).²⁴⁴ Anaphylactic reactions to NSAIDs are unrelated to other reactions caused by these drugs, such as respiratory reactions and exacerbations of chronic idiopathic urticaria.²⁴⁵ 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 medication-specific in that some patients who have had an anaphylactic reaction to one NSAID are able to tolerate structurally unrelated NSAIDs, but this is largely based on clinical experience rather than large-scale challenge studies.²⁴⁴

ANTICANCER CHEMOTHERAPY DRUGS

Anaphylaxis to anticancer chemotherapy drugs is being encountered more frequently because use of these drugs has increased,²⁴⁶ particularly the platinum-containing drugs, such as cisplatin and carboplatin. Skin testing to these agents may be helpful in determining whether sensitivity exists and at what dose to proceed with desensitization if this is necessary.²⁴⁷ In addition, acute anaphylactoid infusion reactions occur in up to 42% of patients treated on first exposure²⁴⁸ for which rapid desensitization is possible.^{249,250} In some instances the solvent in which these drugs are formulated (Cremophor-L) might cause an anaphylactic reaction²⁵¹. Components other than the drug product itself may be the cause of significant reactions with other drugs, such as heparin.²⁵²

BIOLOGICAL MODIFIERS AND MONOCLONAL ANTIBODIES

Anaphylaxis to biological modifiers and monoclonal antibodies has been known to occur.²⁵³ Most notably, there has been concern regarding anaphylactic events that occurred after administration of omalizumab (anti-IgE). In this regard, one hundred twenty-four cases of anaphylaxis were reviewed by the Food and Drug Administration.²⁵⁴ A significant percent of anaphylactic reactions to omalizumab were 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.

The analysis of the post-marketing for omalizumab indicated that the overall frequency of anaphylaxis is approximately 0.09% to 0.2% of treated patients; a frequency higher than reported in the pre-marketing clinical trials database. With these observations in mind, the omalizumab Joint Task Force of the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology issued guidelines regarding the precautions necessary when administering omalizumab.²⁵⁵

The Task Force recommended that: 1) patients should be observed for two hours after the first three 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 following 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 prior to the administration of omalizumab should be made, including vital signs, an assessment of asthma control, and a measurement of lung function.

Cetuximab, a chimeric mouse/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.²⁵⁶ A desensitization protocol has been developed for Cetuximab.²⁵⁷ Anaphylaxis occurs because IgE antibodies develop to galactose α1, 3 galactose present on the Fab portion of the Cetuximab heavy-chain. IgE antibodies have also been demonstrated to this

galactose carbohydrate epitope in meat, which might account for reactions that occur during the first dose.²⁵⁸

ANAPHYLACTOID REACTIONS TO RADIOGRAPHIC CONTRAST MATERIAL (RCM)

Radiographic contrast material (RCM) 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 about 1% of patients who receive RCM. However life-threatening reactions occur with a frequency of less than 0.1% with conventional high-osmolality RCM.^{259,260} Although studies quote a wide spectrum of mortality, a reasonable estimate is one in every 75,000 patients who receive RCM.²⁶¹ With the recent development of lower-osmolality RCM, it appears that the overall risk of anaphylactoid reactions has decreased to about one fifth that of conventional RCM.²⁶²

The prevalence of adverse reactions to RCM appears to be greatest in patients 20 to 50 years of age. When adverse reactions occur, however, they are usually most severe in elderly patients.

Patients who are at greatest risk for an anaphylactoid reaction to RCM are those who have experienced a previous anaphylactoid reaction to RCM. This risk has been reported to be between 16-44%.^{263,264} Even, without a history of a previous anaphylactoid reaction, patients with atopy, asthma, or cardiovascular disease are recognized to be at increased risk of developing such a reaction.²⁶⁵⁻²⁶⁷ There is no evidence that the inorganic iodine levels present in seafood or in topically applied iodine-containing solutions are related to adverse events from RCM.

Anaphylactoid reactions have occurred when RCM is used for hysterosalpingograms, myelograms, and retrograde pyelograms.²⁶³ With the use of a pretreatment protocol and the use of lower-osmolality agents, the risk can be reduced to approximately 1%.²⁶⁸

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.²⁶⁶

Pretreatment regimens for prevention of repeat anaphylactoid reactions have consisted of oral glucocorticosteroids, H1 and H2 antihistamines, and other medications, such as ephedrine. A regimen that has been commonly recommended in the past has been 50 mg of prednisone given orally 13, 7, and 1 hours before administration of RCM; 50 mg of diphenhydramine given orally or intramuscularly 1 hour before the administration of RCM; and 25 mg of ephedrine given orally 1 hour before RCM administration. Modifications to this regimen have included lower doses of glucocorticosteroids, oral rather than intramuscular diphenhydramine, the use of other H1 antihistamines, addition of H2 antihistamines, and/or exclusion of ephedrine. 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 every 4 hours until the RCM is administered, and 50 mg of diphenhydramine administered intramuscularly 1 hour before RCM.²⁶⁷

In a setting in which RCM is being administered, a differential diagnosis might include adult respiratory distress syndrome or noncardiogenic pulmonary edema. If a standard pretreatment

regimen fails to prevent what appears to be an anaphylactoid reaction, noncardiogenic pulmonary edema, in particular, should be considered.²⁶⁸ RCM can also expand intravascular volume and precipitate cardiogenic pulmonary edema in patients with ischemic cardiac disease.

STINGING INSECT HYPERSENSITIVITY

Summary Statements

- 85. Anaphylaxis to insect stings has occurred in 3% of adults and 1% of children who have been stung, and can be fatal even on the first reaction. B**
- 86. Cutaneous systemic reactions are most common in children, hypotensive shock is most common in adults, and respiratory manifestations occur equally in all age groups. B**
- 87. The chance of a systemic reaction to a sting is low (5-10%) in patients who have large local reactions and in children with mild (cutaneous) systemic reactions. A**
- 88. Venom skin tests are most sensitive for diagnosis but in vitro testing is an important complementary test. A**
- 89. The degree of sensitivity on skin or in vitro tests does not reliably predict the severity of a sting reaction. B**
- 90. Since asymptomatic venom sensitization can be detected in up to 25% of adults, diagnosis cannot be made on skin testing alone; the history is essential. C**
- 91. Patients discharged from emergency care of anaphylaxis should be given or prescribed auto-injectable epinephrine and receive instruction in its proper use and indications for use as well as advised to set-up an appointment with an allergist-immunologist. Patients should understand, however, that using auto-injectable epinephrine is not a substitute for emergency medical attention. A**
- 92. Venom immunotherapy (VIT) should be recommended for patients with systemic sensitivity to stinging insects as this treatment is highly (90% to 98%) effective. B**
- 93. Most patients can discontinue VIT after 5 years, with low residual risk of a severe sting reaction. A**
- 94. There is a need to develop tests that are: 1) markers of susceptibility that can serve as a screening test to identify patients at high risk of sting anaphylaxis; and 2) markers of tolerance induction to identify patients who can safely discontinue venom immunotherapy. D**

Stinging insects of the order Hymenoptera can cause systemic allergic reactions^{211,269-278} 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 IgE-mediated, but carry a relatively low risk of anaphylaxis from future stings.²¹¹ Systemic (generalized) reactions may include any one or more of the signs and symptoms of anaphylaxis.^{279,282-286} Systemic reactions involving only cutaneous manifestations do not strictly fit the definition of anaphylaxis but are discussed here because they must be considered in the diagnosis and treatment of stinging insect allergy, as potential precursors of anaphylactic reactions.²⁷⁹ Anaphylaxis due to an insect sting differs clinically between children and adults. Cutaneous symptoms and signs are the sole manifestation in only 15% of adults but in more than 60% of children.²⁸⁵ Almost 50% of

reactions in both children and adults include respiratory manifestations. Symptoms and signs of hypotension are uncommon in children but occur in over 60% of adults, with half experiencing loss of consciousness (rare in children).²⁸⁶

Three families of the order Hymenoptera can cause anaphylaxis: the bees (honeybees, bumblebees), vespids (yellow jackets, hornets, wasps), and stinging ants (genus *Solenopsis*). There have been increasing reports of anaphylaxis due to other species of stinging ants in Asia and Australia.²⁸⁷ The immunochemical characteristics and immunogenetic relationships of the Hymenoptera venoms have been thoroughly studied.^{288,289} Honeybee venom is immunochemically distinct from the other Hymenoptera, but vespid venoms have a high degree of cross reactivity with each other. The proteins in fire ant venoms are antigenically unique. Fire ant whole body extract, unlike the other Hymenoptera whole body extracts, does show reasonable allergenic activity for diagnostic skin testing and for preventative immunotherapy.²⁸⁹

Systemic allergic reactions to insect stings are reported by up to 3% of adults, and almost 1% of children who have been stung.^{290,291} 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 a previous reaction to an insect sting.²⁸³ Screening for clinically significant hymenoptera sensitivity is complicated by the fact that over 30% of adults stung in the previous 3 months have venom-specific IgE by skin or *in vitro* testing even though most had no history of an allergic reaction to an insect sting.²⁹⁰ Although many of these individuals became negative for venom-specific IgE after 3-6 years, those who remained positive had a 17% frequency of a systemic reaction to a subsequent sting.²⁹²

Systemic reactions can become progressively more severe with each sting, but this is the exception rather than the rule. In prospective sting challenge studies, less than 1% of the patients had a reaction more severe than their previous reaction,^{293,294} although in retrospective surveys more severe reactions were noted in a larger percent of patients.^{284,295}

Clinical features of anaphylaxis from an insect sting are identical to those due to other causes of anaphylaxis. If the patient experiences a large local reaction to an insect sting, in the absence of a systemic response, venom immunotherapy (VIT) is not usually necessary, although patients with large local reactions are at increased risk for a systemic reaction (5 to 10%).²⁹⁶ In children, a systemic reaction consisting of urticaria alone does not always mandate VIT, although such reactions may be potential precursors of an anaphylactic reaction with subsequent stings. Patients with severe reactions to insect stings should be evaluated for the presence of systemic mast cell disease.²¹¹

Diagnostic tests are indicated in patients who have had systemic reactions to insect stings.^{297,298} The preferred diagnostic method is venom skin testing because of its high degree of sensitivity and proven safety.²⁷¹ Skin test results are positive in 65-85% of patients with a convincing history. Venom skin tests also show unexplained variability over time so that tests can be negative on one occasion and positive on another.²⁹⁹

A negative skin test 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 may occur. In this situation, skin tests may have to be repeated after one to six months.²⁶⁹ 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 may be useful when skin tests cannot be done or when skin tests are negative in a patient with a history of a systemic reaction (2712).

Some investigators have suggested that sting challenge is the most specific diagnostic test, but others find this unethical and impractical.^{294,300,301} Furthermore, a single negative challenge sting does not preclude anaphylaxis to a subsequent sting.^{293,302}

Toxic reactions due to massive envenomation from multiple stings estimated to be greater than 100,²⁵⁴ might be clinically indistinguishable from allergic reactions since mediators can produce physiologic effects which mimic those produced from an allergic reaction.

Individuals who are allergic to stinging insects should avoid areas with a high risk of exposure, particularly outdoor settings with foods and drinks that may attract stinging insects. However, excessive fear can impair a patient's quality of life and needs to be included in the considerations for venom immunotherapy.²⁸⁰ Auto-injectible epinephrine should be provided to any patient who has experienced a systemic reaction to an insect sting, with the exception of children who have experienced only a cutaneous reaction.

In placebo-controlled trials venom immunotherapy (VIT) was 90-98% effective in completely preventing systemic reactions to stings.²⁷²⁻²⁷⁴ The indications for VIT are a history of a systemic allergic reaction to a sting and a positive diagnostic test for venom-specific IgE. Those with a recent history of anaphylaxis from an insect sting and a positive skin test have a 30% to 70% chance of a systemic reaction to a subsequent sting.^{273,294,303} VIT is not required when the chance of a systemic reaction is <10%, as in large local reactors and children with cutaneous systemic reactions, but still may be considered in this setting.³⁰⁴⁻³⁰⁷

Therapy is 98% effective in completely preventing a systemic allergic reaction to a sting when treatment includes mixed vespid venoms (300 mcg total dose), but complete protection is achieved in only 75% to 85% of patients utilizing 100 mcg of any single venom (e.g., honeybee, yellow jacket or *Polistes* wasp).²⁷⁵⁻²⁷⁷ Fire ant immunotherapy using whole body extracts has been reported to be reasonably safe and effective, although no controlled studies have been performed. 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.³⁰⁸

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.^{274,275}

Immunotherapy with whole body extract of fire ant has been shown to be safe and effective for treatment of patients who have had a systemic reaction to a fire ant sting, although there have been no controlled trials demonstrating safety and efficacy.^{276,277} See updated parameter on stinging insect hypersensitivity.

In a retrospective study of patients experiencing anaphylaxis from hymenoptera venom,³⁰⁹ ACE inhibitor exposure was associated with statistically significant increase in risk for more severe anaphylaxis (OR = 2.27, 95% CI = 1.13-4.56, p = .019). As ACE inhibitors are frequently prescribed for patients with cardiovascular disease, a tenable interpretation of these data is that ACE inhibitor exposure is a marker for patients with more severe cardiovascular disease. On the other hand, as ACE inhibitors may indeed enhance risk for more severe anaphylaxis, based on these data and previously published case reports,³¹⁰ it is prudent to consider ACE inhibitor suspension to reduce risk for untoward

outcomes in patients with anaphylactic potential to hymenoptera venom and/or receiving venom immunotherapy, while supplanting the ACE inhibitor with an equally efficacious non ACE inhibitor alternative, as feasible. For patients who require an ACE inhibitor for an indication for which there is no equally effective alternative available, a management decision by the physician prescribing venom immunotherapy should be approached cautiously on an individualized risk-benefit basis.

PREVENTION OF ANAPHYLAXIS

Summary Statements

95. Avoidance management should be individualized, taking into consideration factors such as age, activity, occupation, hobbies, residential conditions, access to medical care, and the patients' level of personal anxiety. C
96. Even in cases when the allergen is known, avoidance measures may not always be successful. Therefore, patients should be instructed in self-management of anaphylaxis. C
97. Venom immunotherapy (VIT) is successful in preventing anaphylaxis in up to 98% of patients who have previously experienced venom-induced anaphylaxis. A
98. Pharmacologic prophylaxis should be used in select situations, e.g. to prevent recurrent anaphylactic reactions to radiographic contrast material and fluorescein, as well as to prevent idiopathic anaphylaxis. In these specific situations, prophylaxis with glucocorticosteroids and antihistamines markedly reduces the occurrence of subsequent reactions. C
99. Desensitization to medications that are known to have caused anaphylaxis can be effective. The desensitization is temporary, and if the medication is required in the future, the desensitization process must be repeated. C
100. Patient education might be the most important preventive strategy. Education can emphasize hidden allergens, cross-reactivity between various allergens and drugs, unforeseen risks during medical procedures, and when and how to use self-administered epinephrine. Physicians should educate patients about the risks of future anaphylaxis, as well as the benefits of avoidance measures. B

Patients should be educated regarding avoidance measures for known or suspected triggers of anaphylaxis. This should take into consideration factors such as age, concomitant conditions, activity, occupation, hobbies, residential conditions, access to medical care, as well as and the patient's level of personal anxiety. Education should emphasize hidden allergens, cross-reactivity between various allergens and drugs, 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 auto-injectible epinephrine, with an understanding that these measures are not a substitute for emergency medical attention during anaphylaxis.³¹¹ Following emergency treatment, the patient should be seen in consultation by an allergist/immunologist to review potential causes, prevention, and treatment of subsequent episodes.

Awareness of the risk factors for anaphylaxis is important in preventing the occurrence of such reactions. Recognition of major

risk factors for anaphylaxis include, but are not limited to: a prior history of such reactions; patient exposure to the possible trigger(s); and atopic background. An atopic background may be a risk factor for stinging insect and latex-induced anaphylaxis (and possibly anaphylactoid reactions to radiographic contrast material) but not for anaphylactic reactions to medications. This is particularly important in regard to avoidance by the patient of possible triggers. Avoidance measures can be successful in any given patient if future exposure to allergens which have been shown to produce anaphylaxis in that patient can be prevented. However, avoidance measures must be individualized, taking into consideration patient age, activity, occupation, hobbies, residential conditions, access to medical care, and the patients' level of personal anxiety.

Patients who will be exposed to known triggers of a prior reaction can in some cases be protected by: 1) pharmacologic prophylaxis; 2) allergen immunotherapy; or 3) desensitization. Pharmacologic prophylaxis can be used to prevent recurrent anaphylactic/anaphylactoid reactions to radiographic contrast material and fluorescein, as well as idiopathic anaphylaxis.

Physicians should educate patients about the risks of future anaphylaxis, as well as the benefits of avoidance measures. The prevention of anaphylaxis is aided by the patients having medic alert identification.

At times, a preventative protocol may be of benefit. For example, a pretreatment regimen has been successfully employed to prevent reactions to radiocontrast material in patients who have previously reacted to this diagnostic agent.

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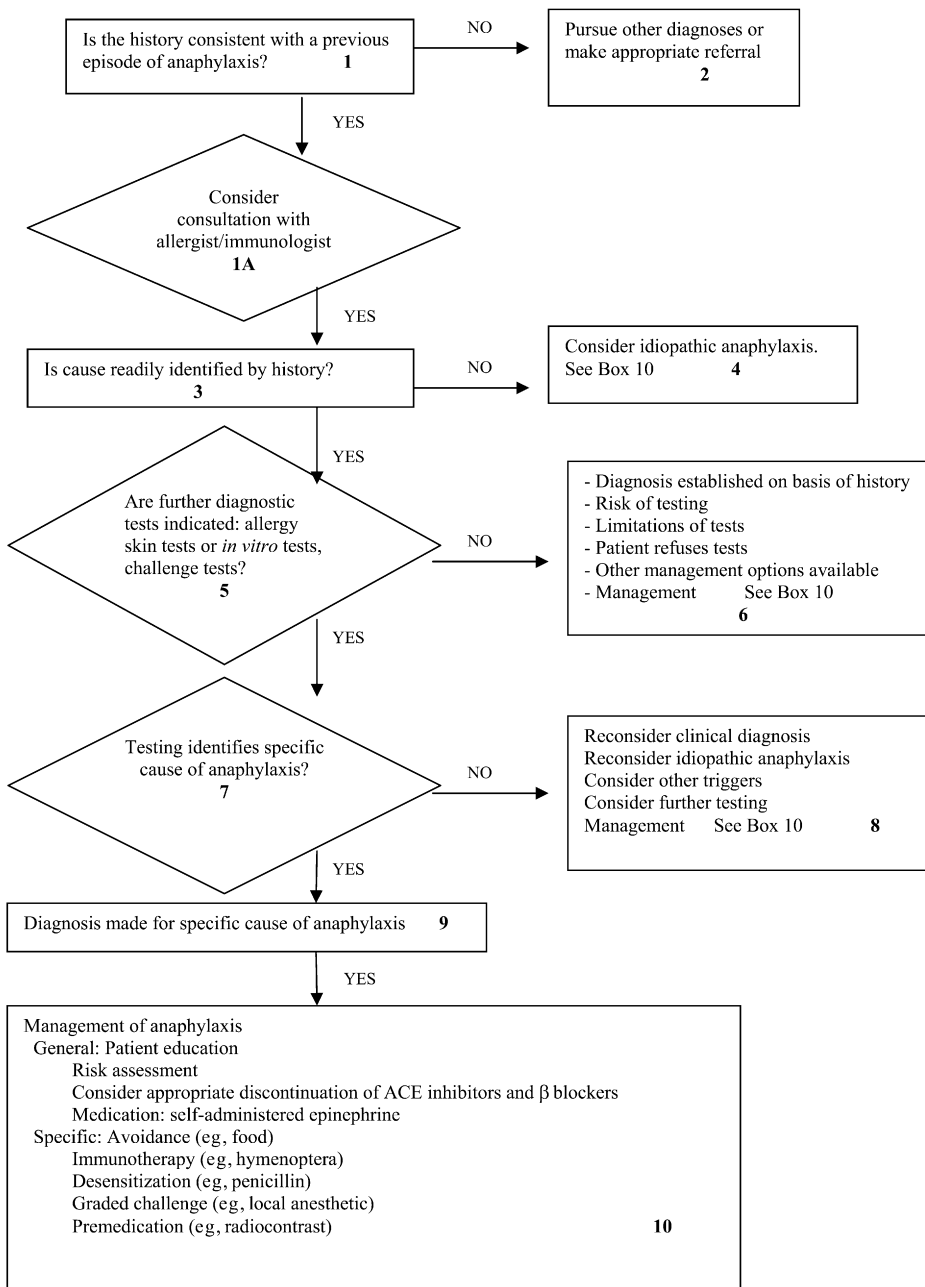


FIG E1. Algorithm for initial evaluation and management of a patient with a history of a previous episode of anaphylaxis.

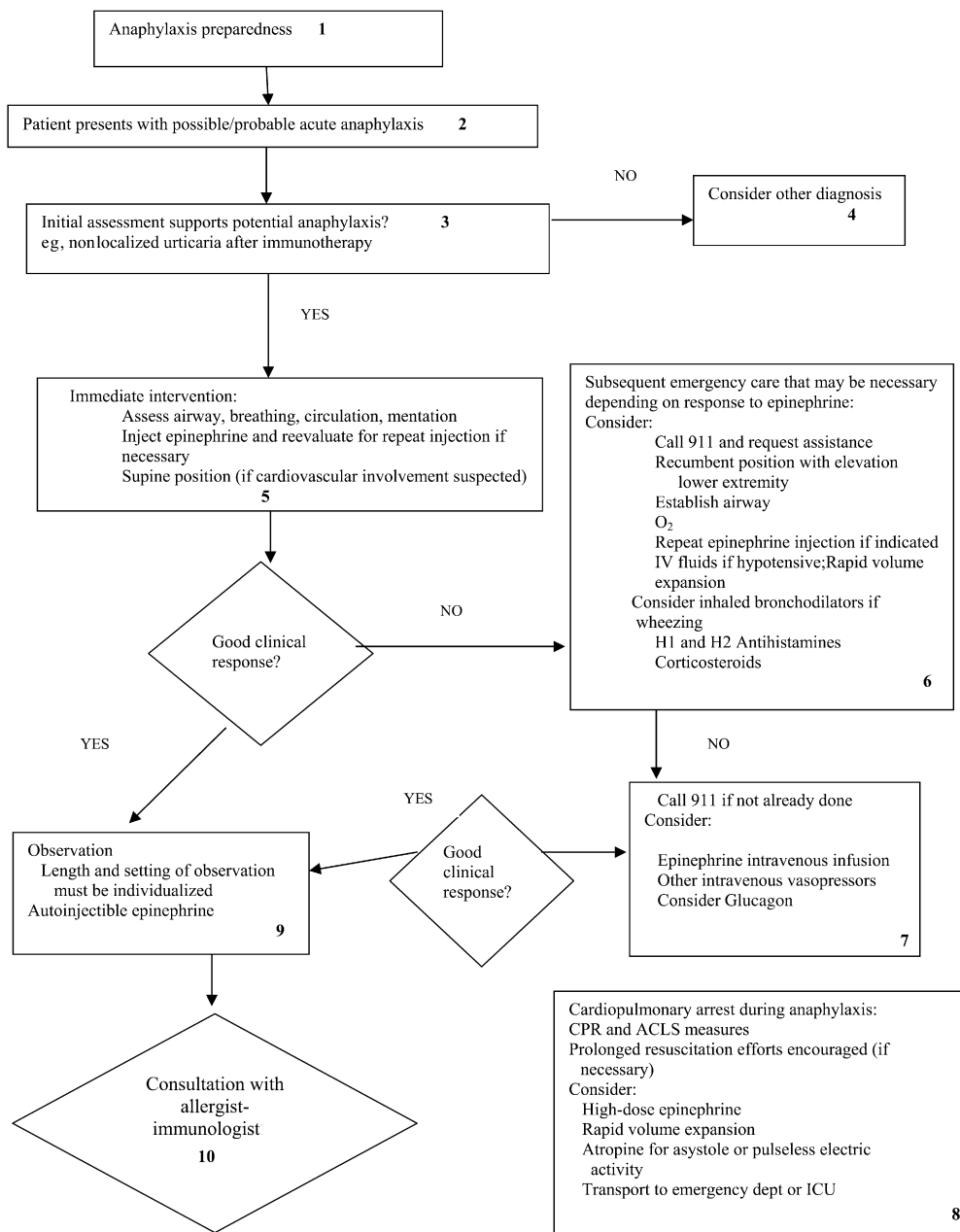


FIG E2. Algorithm for the treatment of an anaphylactic event in the outpatient setting. *IV*, Intravenous.

___ Flowsheet for recording clinical, symptoms signs and treatments
 ___ Emergency Treatment Protocol ___ BP cuff/monitor^ ___ Stethoscope ___ Tourniquet

VENTILATION AND OXYGEN DELIVERY^^

___ Disposable Facemask
 ___ Infant
 ___ Toddler
 port
 ___ Child/Small Adult
 ___ Adult
 Ambubag)
 Ambubag)
 ___ Nasal Cannula (adult)
 ___ Oropharyngeal airways
 ___ 6cm
 ___ 7cm
 ___ 8cm
 ___ 9cm
 ___ 10cm

___ O₂ E-cylinder w/wrench; >1100 psi (>1/2 full)
 ___ Extension tubing
 ___ Adult pocket mask with extension
 ___ Pediatric oxygen mask
 ___ Adult Self-Inflating bag (ie.
 ___ Pediatric Self-inflating bag (ie.

MEDICATIONS

Epinephrine * ^^

___ Epinephrine 1:1000 1 mL ampules (3)
 ___ Epinephrine 1:1000 multidose vial

___ 0.9% normal saline
 ___ 5% dextrose (one 250mL bag for admixture)

Antihistamines ^^

___ Diphenhydramine (Benadryl) 50 mg/mL IV
 ___ Benadryl liquid 12.5 mg/5 mL
 ___ Ranitidine (Zantac) 25 mg/mL IV

Intravenous Delivery System
 ___ Macrodrip administration sets, 10-15 drops/mL
 ___ Minidrip set, 60 drops/mL (for dopamine)
 ___ Connection tubing

Systemic Corticosteroids ^^

___ Prednisone 10mg tablets
 ___ Prednisolone syrup 15 mg/mL
 ___ Methylprednisolone (Solumedrol) 125mg vial

___ Three-way stopcock
 ___ Catheter needles gauge 16, 18, 20, 22
 ___ Butterfly needles gauge 19, 21

Other Therapeutic Agents^^^

___ Glucagon 1mg/mL vial
 ___ Atropine 0.5 mg/mL IV
 ___ Albuterol inhalation solution, 0.5%
 ___ Dopamine 200 mg/5 mL (2 ampules)

___ Syringes w/needles 1mL, 10mL, 20mL
 ___ Angiocath 16, 18 gauge
 ___ 1" synthetic tape (eg, Transpore)
 ___ Latex-free gloves
 ___ Alcohol swabs (box)
 ___ IV Pole

* Required for treatment of anaphylaxis

^A minimum of 3 cuff sizes should be available (child, adult, obese/large adult).

^^ Where several options are listed under general headings, a physician should determine which supplies are required and appropriate to his/her practice.

^^^Agents to be considered, but by no means mandatory

Replace supplies within one month of expiration date. Check supplies monthly and restock after use. Oxygen tank and connections should be checked periodically for air leak or malfunction.

Note: Not all items need to be present in each treatment setting.

Initials: _____

Date: _____

Modified with permission from: Kemp SF. "Anaphylaxis Committee Proposals to Improve Safety of Skin Testing and Immunotherapy Administration". *Allergen Immunotherapy: Increasing Effectiveness and Safety with Specific Measures to Improve Standardized Materials, Methods, Forms and Procedures*. Symposium, 58th Annual Meeting of the American Academy of Allergy, Asthma and Immunology, New York, New York, March 2, 2002.

FIG E3. Suggested anaphylaxis supply check sheet. *BP*, Blood pressure; *IV*, intravenous.

Name _____ Date _____
 Date of Birth _____ Prescribing
 Physician _____

Prior systemic rxn: _____ Hx of asthma? _____
 Date/time of rxn: _____

History of the systemic reaction (SR):

Immediate measures:
 ___ Assess airway, breathing, circulation, and orientation
 ___ Injectable Epinephrine
 ___ Activate EMS (call 911 or local rescue squad) Y/N Time called: _____ AM/PM
 ___ Management algorithm reviewed (as needed)

Signs & Symptoms (Circle pertinent findings):

Respiratory:	Skin:	Eye/Nasal:	Vascular:	Other:
Dyspnea, chest tightness	Urticaria	Runny nose	Hypotension	Difficulty swallowing
Wheezing	Angioedema	Red eyes	Chest discomfort	Abdominal pain, nausea, emesis, diarrhea
Cough	Generalized itch	Congestion	Dizziness, syncope	Diaphoresis
Stridor	Flushing	Sneezing	Headache	Apprehension

Time	Resp. rate/	Pulse/	Intervention, Meds,	PEFR

Time (AM/PM)/ Condition upon release: _____

Patient instructions: _____

Follow-up call to patient: Time _____

Comments: _____

Clinical impression: _____ **True SR**

Signatures _____ RN _____ MD/DO

Modified with permission from: Kemp SF. "Anaphylaxis Committee Proposals to Improve Safety of Skin Testing and Immunotherapy Administration". *Allergen Immunotherapy: Increasing Effectiveness and Safety with Specific Measures to Improve Standardized Materials, Methods, Forms and Procedures*. Symposium, 58th Annual Meeting of the American Academy of Allergy, Asthma and Immunology, New York, New York, March 2, 2002. Original modified with permission from form used by Linda Cox, MD, Ft. Lauderdale, Florida.

FIG E4. Anaphylaxis treatment record. *BP*, Blood pressure; *rxn*, reaction; *Hx*, history; *EMS*, Emergency Medical Services; *Resp*, respirations; *PEFR*, peak expiratory flow rate.

TABLE E1. Frequency of occurrence of signs and symptoms of anaphylaxis* †‡

Signs and Symptoms	Percent
Cutaneous	
Urticaria and angioedema	85-90
Flushing	45-55
Pruritus without rash	2-5
Respiratory	
Dyspnea, wheeze	45-50
Upper airway angioedema	50-60
Rhinitis	15-20
Dizziness, syncope, hypotension	30-35
Abdominal	
Nausea, vomiting, diarrhea, cramping pain	25-30
Miscellaneous	
Headache	5-8
Substernal pain	4-6
Seizure	1-2

*On the basis of a compilation of 1865 patients reported in references.^{1 through 14}

†Percentages are approximations.

‡Children may have a lower frequency of cutaneous symptoms in anaphylaxis.

TABLE E2. Differential diagnosis of anaphylaxis

Reactions caused by the excess endogenous production of histamine
Systemic mastocytosis
Urticaria pigmentosa
Basophilic leukemia
Acute promyelocytic leukemia with retinoic acid treatment
Hydatid cyst
Vasodepressor (vasovagal) reactions
Other forms of shock
Hemorrhagic
Hypoglycemic
Cardiogenic
Endotoxic
Flushing disorders
Rosacea
Carcinoid
Red man syndrome as a result of vancomycin
Postmenopausal
Alcohol-induced
Unrelated to drug ingestion
Related to drug ingestion
Medullary carcinoma thyroid
Autonomic epilepsy
Vasointestinal peptide and other vasoactive peptide-secreting gastrointestinal tumors
Ingestant-related reactions mimicking anaphylaxis (restaurant syndromes)
Monosodium glutamate
Sulfites
Scombroidosis
Miscellaneous
C1 esterase deficiency syndromes (acquired and hereditary angioedema)
Pheochromocytoma
Neurologic (seizure, stroke)
Capillary leak syndrome
Panic attacks
Vocal cord dysfunction syndrome

TABLE E3. Laboratory tests to be considered in the differential diagnosis of anaphylaxis

To be measured	Comment
Serum tryptase	Serum tryptase levels peak 60-90 min after the onset of anaphylaxis and persist to 6 h. Ideally the measurement should be obtained between 1 and 2 h after the initiation of symptoms.
Plasma histamine	Plasma histamine levels begin to rise within 5-10 min and remain elevated only for 30-60 min. They are of little help if the patient is seen as long as an hour or more after the onset of the event.
24-Hour urinary histamine metabolite (methyl histamine) of time	Urinary histamine and its metabolites are elevated for a longer period – up to 24 h.
Plasma-free metanephrine	To rule out a paradoxical response to a pheochromocytoma.
Urinary vanillylmandelic acid	Also useful in ruling out a paradoxical response to a pheochromocytoma.
Serum serotonin	To rule out carcinoid syndrome.
Urinary 5-hydroxyindoleacetic acid	Also to rule out carcinoid syndrome.
Serum vasointestinal hormonal polypeptide panel including pancreastatin, pancreatic hormone, Vasointestinal Polypeptide, and substance P	Useful to rule out the presence of a vasoactive polypeptide-secreting gastrointestinal tumor or a medullary carcinoma of the thyroid, which also can secrete vasoactive peptides.

TABLE E4. Special considerations for anaphylaxis in children

I.		When is it hypotension?
Age		Systolic blood pressure (mm Hg)
Term neonates (0-28 d)		<60
Infants (1-12 mo)		<70
Children (>1 y to 10 y)		<70 + (2 × age in y)
Beyond 10 y		<90

II. Infusion rates for epinephrine and dopamine in children with cardiac arrest or profound hypotension		
Medication	Dose range	Preparation*
Dopamine	2-20 µg/kg/min	6 × body weight (in kg) = # of mg diluted to total 100 mL saline; then 1 mL/h delivers 1 µg/kg/min
Epinephrine	0.1 µg/kg/min	0.6 × body weight (in kg) = # of mg diluted to total 100 mL saline; then 1 mL/h delivers 0.1 µg/kg/min

*Infusion rates shown use the “rule of 6.” An alternative is to prepare a more dilute or more concentrated drug solution based on a standard drug concentration, in which case an individual dose must be calculated for each patient and each infusion rate, as follows: infusion rate (mL/h) = (weight [kg] × dose [µg/kg/min] × 60 min/h)/concentration (µg/mL).

TABLE E5. 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

TABLE E6. Example of contents of latex-free cart

I.	Glass syringes
II.	Ampules
III.	Tubing without ports (taped ports)
IV.	Stopcocks
V.	Nonlatex stethoscope
VI.	Nonlatex gloves
VII.	Nonlatex breathing system
	Neoprene bags
	Plastic masks
	Nonlatex Ambu
	Uncuffed polyvinyl chloride endotracheal tube
VIII.	Dermicel
IX.	Disposable nonlatex blood pressure cuffs
X.	Webril tourniquets

TABLE E7. Agents frequently implicated in perioperative anaphylaxis and probable mechanisms of adverse reactions

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

TABLE E8. 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†
Thioamyl	0.1*
Thiopental	0.20*
Tubocurarine	0.0003,* 0.001†
Rocuronium	0.01†
Vecuronium	0.004†

*Rose and Fisher (2001)¹²³

†Moscicki et al (1990)¹²²