The diagnosis and management of anaphylaxis: An updated practice parameter

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These parameters were developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology.

The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing "The diagnosis and management of anaphylaxis: an updated practice parameter." This is a complete and comprehensive document at the current time. The medical environment is a changing environment, and not all recommendations will be appropriate for all patients. Because this document incorporated the efforts of many participants, no single individual, including those who served on the Joint Task force, is authorized to provide an official AAAAI or ACAAI interpretation of these practice parameters. Any request for information about or an interpretation of these practice parameters by the AAAAI or ACAAI should be directed to the Executive Offices of the AAAAI, the ACAAI, and the Joint Council of Allergy, Asthma and Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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Published practice parameters of the Joint Task Force on Practice Parameters for Allergy & Immunology include the following:

1. Practice parameters for the diagnosis and treatment of asthma. J Allergy Clin Immunol 1995;96(suppl): S707-S870.
2. Practice parameters for allergy diagnostic testing. Ann Allergy 1995;75:543-625.
3. Practice parameters for the diagnosis and management of immunodeficiency. Ann Allergy 1996;76: 282-94.
4. Practice parameters for allergen immunotherapy. J Allergy Clin Immunol 1996;98:1001-11.
5. Disease management of atopic dermatitis: a practice parameter. Ann Allergy 1997;79:197-211.
6. The diagnosis and management of anaphylaxis. J Allergy Clin Immunol 1998;101(suppl):S465-S528.
7. Algorithm for the diagnosis and management of asthma: a practice parameter update. Ann Allergy 1998;81:415-20.
8. Diagnosis and management of rhinitis: parameter documents of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. Ann Allergy 1998;81(suppl):S463-S518.

9. Parameters for the diagnosis and management of sinusitis. J Allergy Clin Immunol 1998;102(suppl) S107-S144.
10. Stinging insect hypersensitivity: a practice parameter. J Allergy Clin Immunol 1999;103:963-80.
11. Disease management of drug hypersensitivity: a practice parameter. Ann Allergy 1999;83(suppl):S665-S700.
12. Diagnosis and management of urticaria: a practice parameter. Ann Allergy 2000;85(suppl):S521-S544.
13. Allergen immunotherapy: a practice parameter. Ann Allergy 2003;90(suppl):SI-S540.
14. Symptom severity assessment of allergic rhinitis: Part I. Ann Allergy 2003;91:105-114.
15. Stinging insect hypersensitivity: a practice parameter update. J Allergy Clin Immunol 114;4:869-86.

These parameters are also available on the Internet at http://www.jcaai.org.

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

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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 on controlled study without randomization

IIb   Evidence from at least one other type of quasiexperimental study

III   Evidence from nonexperimental 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

NR   Not rated

PREFACE

Anaphylaxis is defined for the purposes of this document as a condition caused by an IgE-mediated reaction. Anaphylactoid reactions are defined as those reactions that produce the same clinical picture as anaphylaxis but are not IgE mediated. Where both IgE-mediated and non–IgE-mediated mechanisms are a possible cause, the term "anaphylactic" has been used to describe the reaction.

Anaphylactic reactions are often life-threatening and almost always unanticipated. Even when there are mild symptoms initially, the potential for progression to a severe and even irreversible outcome must be recognized. Any delay in the recognition of the initial signs and symptoms of anaphylaxis can result in a fatal outcome either because of airway obstruction or vascular collapse.

Most patients who have experienced anaphylaxis should be evaluated by a specialist in allergy-immunology. Such a consultation is appropriate because individuals trained in allergy-immunology possess particular training and skills to evaluate and appropriately treat individuals at risk of anaphylaxis.

The objective of this parameter, "The diagnosis and management of anaphylaxis: an updated practice 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 diagnosis and management of anaphylaxis: an updated practice parameter" was developed by the Joint Task Force on Practice Parameters, which has published 11 practice parameters for the field of allergy-immunology (see list of publications). The 3 national allergy and immunology societies—the American College of Allergy, Asthma and Immunology (ACAAI); the American Academy of Allergy, Asthma and Immunology (AAAAI); and the Joint Council of Allergy, Asthma and Immunology (JCAAI)—have given the Joint Task Force the responsibility for both creating new parameters and updating existing parameters. This parameter builds on "The diagnosis and management of anaphylaxis," which was published in 1998 by the Joint Task Force on Practice Parameters. It was written and reviewed by specialists in the field of allergy and immunology and was exclusively funded by the 3 allergy and immunology organizations noted above.

A workgroup chaired by Phillip Lieberman, MD, prepared the initial draft. The Joint Task Force then reworked the initial draft into a working draft of the document. A comprehensive search of the medical literature was conducted with various search engines, including PubMed, using appropriate search terms. Published clinical studies were rated by category of evidence and used to establish the strength of the clinical recommendations (see "Classification of rating and evidence" above). The working draft of this updated parameter was reviewed by a large number of experts on anaphylaxis selected by the sponsoring organizations. This document represents an evidence-based and broadly accepted consensus viewpoint on the diagnosis and management of anaphylaxis.

"The diagnosis and management of anaphylaxis: an updated practice parameter" contains annotated algorithms that present the major decision points for the initial evaluation and management of a patient with a history of a previous episode of anaphylaxis and for the acute management of anaphylaxis. These are followed by a list of summary statements that represent the key points to consider in the evaluation and management of anaphylaxis. These summary statements can also be found before each section in this document followed by the text that supports the summary statements, which are, in turn, followed by graded references that support the statements in the text. In addition to sections on the diagnosis and management of anaphylaxis, this updated parameter contains sections on anaphylaxis to foods, latex, seminal fluid, allergen immunotherapy, and medications, as well as exercise-induced anaphylaxis, idiopathic anaphylaxis, and anaphylaxis occurring during general anesthesia, both during the intraoperative and postoperative periods.

Among the objectives of this updated parameter are the development of an improved understanding of anaphylaxis among health care professionals, medical students, interns, residents, and fellows, as well as managed care executives and administrators. The parameter is intended to provide guidelines and support for the practicing physician and to improve the quality of care for patients who experience anaphylaxis. The Joint Task Force on Practice Parameters recognizes that there are different, although appropriate, approaches to the diagnosis and management of anaphylactic reactions that often require flexible recommendations. Therefore the diagnosis and management of anaphylactic reactions must be individualized on the basis of unique features in particular patients.

Throughout this document, we will rely on anaphylaxis to imply anaphylactic (IgE-mediated) and anaphylactoid (non–IgE-mediated) reactions.

The Joint Task Force on Practice Parameters wishes to thank the ACAAI, AAAAI, and JCAAI, who have supported the preparation of this updated parameter, and the large number of individuals who have so kindly dedicated their time and effort to the review of this document.

ALGORITHM FOR INITIAL EVALUATION AND MANAGEMENT OF A PATIENT WITH A HISTORY OF ANAPHYLAXIS (Fig 1)

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 might elicit manifestations, such as urticaria, angioedema, flushing, pruritus, upper airway obstruction, gastrointestinal symptoms, syncope, hypotension, lower airway obstruction, and/or dizziness.

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

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

At this point, it should be noted that the absence of cutaneous symptoms puts the diagnosis in question because the majority of anaphylaxis includes cutaneous symptoms, but their absence would not necessarily rule out an anaphylactic or anaphylactoid event.

The history should concentrate on agents encountered before the reaction. Whenever appropriate, the information should be obtained from not only the patient but also family members or other witnesses. The complete sequence of events must be reviewed, with special attention paid to the 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 (eg, serum tryptase levels) might be helpful in making the diagnosis of anaphylaxis or distinguishing it from other entities.
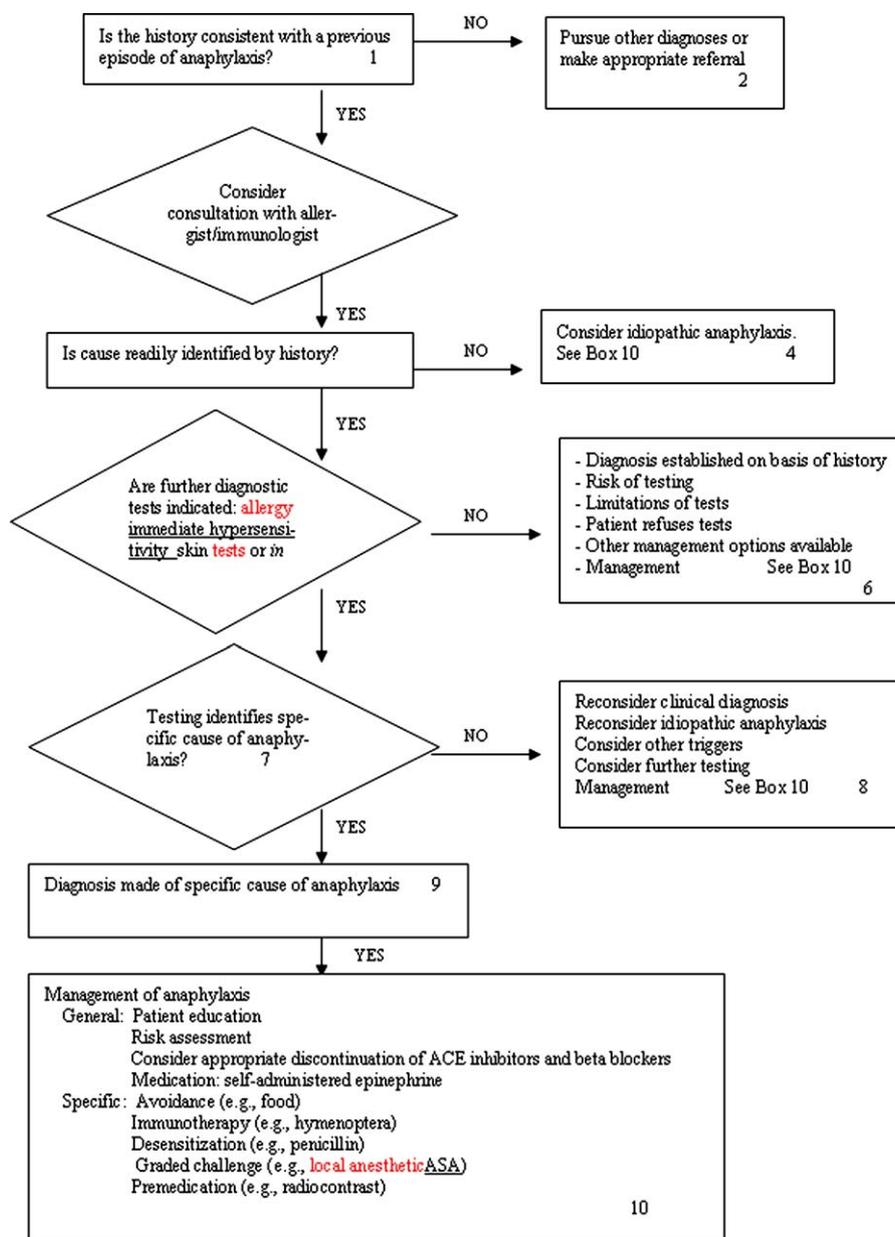
FIG 1. Algorithm for the initial evaluation and management of a patient with a history of an episode of anaphylaxis. *ACE*, Angiotensin-converting enzyme.

Annotation 1A: Consider consultation with an allergist-immunologist

Patients with anaphylaxis might be first seen with serious and life-threatening symptoms. 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 the following: (1) vasodepressor (vasovagal-neurocardiogenic) syncope; (2) syndromes that can be associated with flushing (eg, metastatic carcinoid); (3) postprandial syndromes (eg, scombroid poisoning); (4) systemic mastocytosis; (5) psychiatric disorders that can mimic anaphylaxis, such as panic attacks or vocal cord dysfunction syndrome; (6) angioedema (eg, hereditary angioedema); (7) other causes of shock (eg, cardiogenic); and (8) other cardiovascular or respiratory events.

Annotation 3: Is cause readily identified by history?

The history is the most important tool to establish the cause of anaphylaxis and takes precedence over diagnostic tests. A detailed history of all ingestants (both foods and drugs) several hours before the episode should be obtained. In addition, the labels for all packaged foods ingested by the patient in this period of time should be reviewed because a substance added to the food (eg, carmine) could be responsible. A history of any preceding bite or sting should be obtained. The patient's activities (eg, exercise, sexual activity, or both) preceding the event should be reviewed. Patient diaries might be a useful adjunct in confirming and 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: immediate hypersensitivity or *in vitro* tests, challenge tests?

Immediate hypersensitivity tests or *in vitro* specific IgE tests and/or challenge tests might be appropriate to help define the cause of the anaphylactic episode. However, the history might be so specific that none of the above 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 might be circumstances in which allergy skin tests, *in vitro* specific IgE tests, and/or challenge tests might not be warranted. In general, this might apply when the clinician (with the consent of the patient) decides to proceed with management on the basis of the history and physical examination.

For example, the clinical history of anaphylaxis to a specific agent might be so strong that testing is unnecessary (or dangerous). Conversely, the medical history of anaphylaxis might be sufficiently mild or weak that management can proceed in the absence of testing. If avoidance can be easily and safely accomplished, testing might not be necessary.

Furthermore, testing or challenge with reagents to a suspected allergen might not be available, or the accuracy of the test might be in question. In addition, for patients with a history of anaphylaxis, challenge tests (and, to a lesser extent, skin tests) might be hazardous.

Annotation 7: Testing identifies specific cause of anaphylaxis

Skin tests or *in vitro* tests that determine the presence of specific IgE antibodies can identify specific causes of anaphylaxis. Causes of anaphylaxis that can be defined in this way include foods, medications (eg, penicillin and insulin), and stinging insects. For the majority of medications, standardized testing either by *in vivo* or *in vitro* means is not available. Such tests are only valid when the reaction is due to a true anaphylactic event (IgE-mediated reaction) and not as a result of an anaphylactoid (non–IgE-mediated) reaction.

In general, skin testing is more sensitive than *in vitro* testing and is the diagnostic procedure of choice for evaluation of most potential causes of anaphylaxis (eg, penicillin, insect stings, and foods). It is essential that the correct technique for skin testing be used to obtain meaningful data regarding causative agents of anaphylaxis. When possible, standardized extracts should be used (occasionally fresh food extracts will be superior to available standardized extracts). If the skin testing extract has not been standardized (eg, latex, protamine, or antibiotics other than penicillin), the predictive value is 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 test or *in vitro* test results depends on the ability to correlate such results with the patient's history.

If tests for specific IgE antibodies (ie, 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 might also be appropriate in patients with anaphylactoid reactions (eg, reactions to aspirin or other nonsteroidal anti-inflammatory drugs). Challenges 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 trigger factors and diagnoses. The medical history and laboratory test results should be reviewed. Further testing for specific IgE antibodies should be considered. Laboratory studies that might be helpful include serum tryptase measurement, as well as urinary 5-hydroxyindoleacetic acid, methylhistamine, and catecholamine measurement. Idiopathic anaphylaxis is a diagnosis of exclusion (see ''Idiopathic anaphylaxis'').

Management of anaphylaxis episodes should follow annotation 10 (see algorithm).

Annotation 9: Diagnosis made of specific cause of anaphylaxis

The diagnosis of a specific cause of anaphylaxis might 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 (eg, food, medication, or insect sting), patients should be educated about agents or exposures that would place them at risk for future reactions and be counseled on avoidance measures that might 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 might be helpful to educate patients about applicable management options (eg, medication pretreatment and use of low-osmolarity agents in patients with a history of reactions to radiographic contrast media or desensitization for drugs, such as antibiotics). Patients who have had anaphylactic reactions to insect stings should be advised about avoidance measures to reduce the risk of insect stings are candidates for insect venom immunotherapy (see ''Stinging insect hypersensitivity: a practice parameter update''). Patients who have had anaphylaxis should carry self-injectable epinephrine for use if anaphylaxis develops. There might be exceptions to this (eg, anaphylaxis to penicillin). Patients should also carry identification indicating that they are prone to anaphylaxis and indicating the responsible agent. Patients taking β-blockers are at increased risk during anaphylaxis.

ALGORITHM FOR THE TREATMENT OF ACUTE ANAPHYLAXIS (Fig 2)

Annotation 1. Anaphylaxis preparedness

It is important to stress that management recommendations are subject to physician discretion and that variations in sequence and performance rely on physician judgment. Additionally, 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. Preparedness, prompt recognition, and appropriate and aggressive treatment are integral to parts of successful management of anaphylaxis. A treatment log will assist in accurately recording progress (Fig 3).

Recommendations depend on practice resources and the proximity to other emergency assistance. Stocking and maintaining anaphylaxis supplies with regular written documentation of contents 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 ''Management of anaphylaxis'' [Fig 4]. Not all items need to be present in each office.)

Regular anaphylaxis practice drills, the contents of which are left to the discretion and qualifications of the individual physician, are strongly recommended. Essential ingredients are identification of a person who will be responsible for calling emergency medical services and the person who will document treatment and time each is rendered. The emergency kit should be up to date and complete. Everyone who will be directly involved in patient care should, for example, be able to easily locate necessary supplies and rapidly assemble fluids for intravenous administration.

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 (anaphylactoid reactions are IgE independent), that results from the sudden systemic release of mast cells and basophil mediators. It has varied clinical presentations, but respiratory compromise and cardiovascular collapse cause the most concern because they are the most frequent causes of fatalities. Urticaria and angioedema are the most common manifestations of anaphylaxis but might be delayed or absent in rapidly progressive anaphylaxis. The more rapidly 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 (see comments in text), but some reactions might develop later (eg, >30 minutes after exposure). Late-phase or biphasic reactions, which occur 8 to 12 hours after the initial attack, have also been reported. Protracted and severe anaphylaxis might last up to 32 hours, despite aggressive treatment.

Increased vascular permeability, a characteristic feature of anaphylaxis, allows transfer of as much as 50% of the intravascular fluid into the extravascular space within 10 minutes. As a result, hemodynamic collapse might occur rapidly with little or no cutaneous or respiratory manifestations.

Annotation 3. Initial assessment supports potential anaphylaxis

Initial assessment should determine whether history and physical findings are compatible with anaphylaxis. The setting of the episode and the history might suggest or reveal the source of the reaction. Evaluation should include level of consciousness (impairment might reflect hypoxia), upper and lower airways (dysphonia, stridor, cough, wheezing, or shortness of breath), cardiovascular system (hypotension with or without syncope and/or
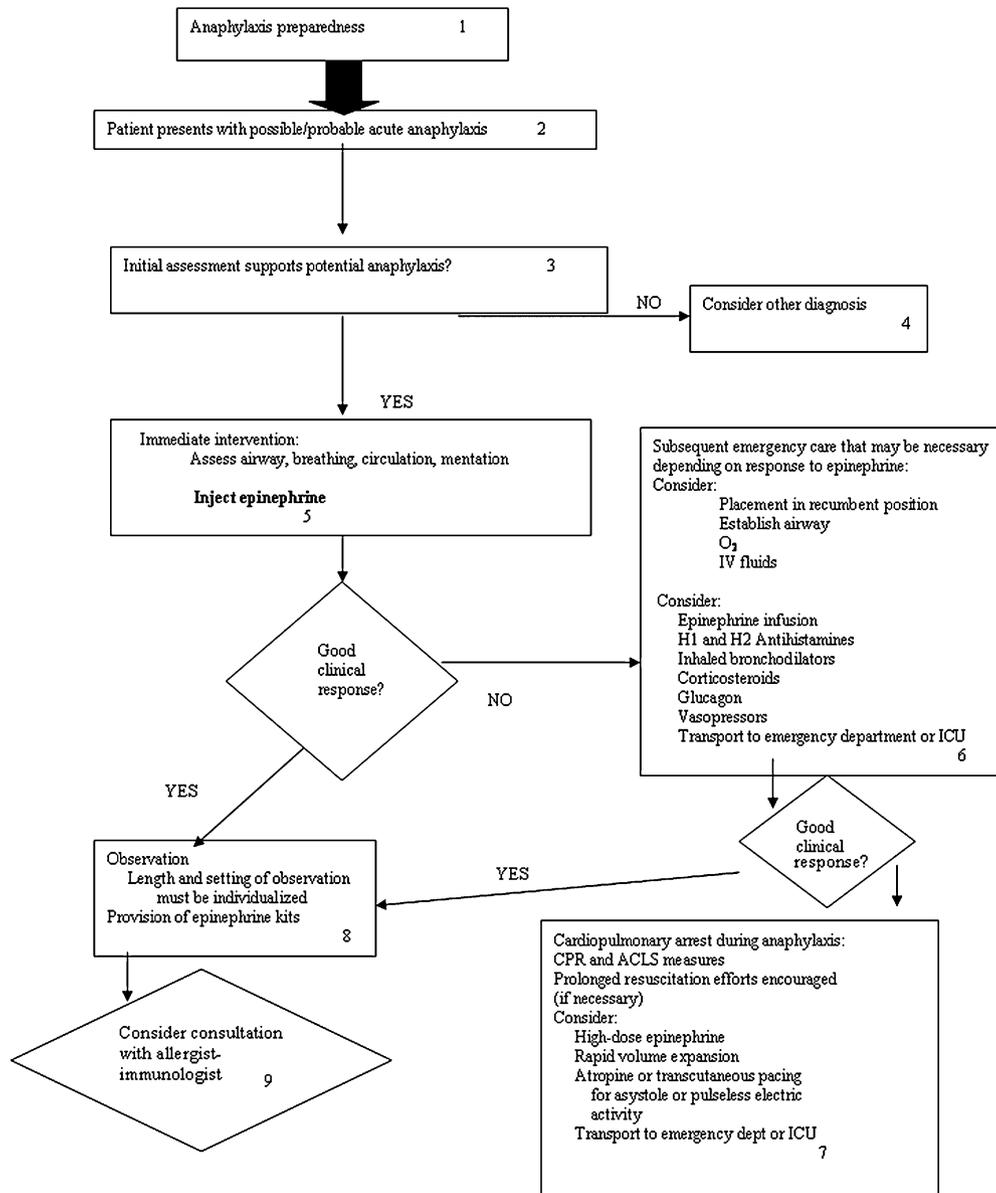
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┌────────────────────────────────────────┐
│ Anaphylaxis preparedness          1     │
└────────────────────────────────────────┘
                  ⬇
┌────────────────────────────────────────────┐
│ Patient presents with possible/probable     │
│ acute anaphylaxis                     2      │
└────────────────────────────────────────────┘
                  │
┌────────────────────────────────────────────┐
│ Initial assessment supports potential        │        NO    ┌──────────────────────────┐
│ anaphylaxis?                          3      │─────────────▶│ Consider other diagnosis  │
└────────────────────────────────────────────┘              │                     4    │
                  │ YES                                       └──────────────────────────┘

┌──────────────────────────────────────┐    ┌──────────────────────────────────────────────┐
│ Immediate intervention:               │    │ Subsequent emergency care that may be         │
│  Assess airway, breathing,            │    │ necessary depending on response to            │
│  circulation, mentation               │    │ epinephrine:                                  │
│                                       │    │ Consider:                                     │
│  Inject epinephrine                   │    │        Placement in recumbent position        │
│            5                          │    │        Establish airway                       │
└──────────────────────────────────────┘    │        O₂                                     │
                  │                          │        IV fluids                              │
                  │                          │                                               │
            ◇ Good clinical ◇               │ Consider:                                     │
            ◇  response?    ◇───────NO─────▶│        Epinephrine infusion                   │
                  │ YES                      │        H1 and H2 Antihistamines               │
                  │                          │        Inhaled bronchodilators                │
                  │                          │        Corticosteroids                        │
                  │                          │        Glucagon                               │
                  │                          │        Vasopressors                           │
                  │                          │        Transport to emergency department      │
                  │                          │        or ICU                          6      │
                  │                          └──────────────────────────────────────────────┘
                  │                                           │
┌──────────────────────────────────┐                  ◇ Good clinical ◇
│ Observation                       │◀──────YES───────◇  response?    ◇
│  Length and setting of observation │                        │
│  must be individualized           │                        │
│ Provision of epinephrine kits     │     ┌──────────────────────────────────────────────┐
│                        8          │     │ Cardiopulmonary arrest during anaphylaxis:    │
└──────────────────────────────────┘     │ CPR and ACLS measures                         │
                  │                        │ Prolonged resuscitation efforts encouraged    │
          ◇ Consider      ◇               │ (if necessary)                                │
          ◇ consultation  ◇               │ Consider:                                     │
          ◇ with allergist-◇              │        High-dose epinephrine                  │
          ◇ immunologist 9 ◇              │        Rapid volume expansion                 │
                                           │        Atropine or transcutaneous pacing      │
                                           │           for asystole or pulseless electric  │
                                           │           activity                            │
                                           │        Transport to emergency dept or ICU     │
                                           │                                       7       │
                                           └──────────────────────────────────────────────┘
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FIG 2. Algorithm for the treatment of acute anaphylaxis. *ICU*, Intensive care unit; *CPR*, cardiopulmonary resuscitation; *ACLS*, advanced cardiac life support.

cardiac arrhythmias), the skin (diffuse or localized erythema, pruritus, urticaria, and/or angioedema), and the gastrointestinal system (nausea, vomiting, or diarrhea). In addition, some patients might have symptoms of lightheadedness, headache, uterine cramps, feeling of impending doom, and unconsciousness.

The vasodepressor (vasovagal) reaction probably is the condition most commonly confused with anaphylactic and anaphylactoid 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 usually normal or increased, and the skin is typically cool and pale. Tachycardia is the rule in anaphylaxis, but it might be absent in patients with conduction defects, with increased vagal tone caused by a cardioinhibitory (Bezold-Jarisch) reflex, or 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. Like anaphylaxis, several conditions might cause abrupt and dramatic patient collapse. Among conditions to consider are vasodepressor (vasovagal) reactions, acute anxiety (eg, panic attack or hyperventilation syndrome), myocardial dysfunction, pulmonary embolism, systemic mast cell disorders, foreign-body aspiration, acute poi-

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

Resp. rate/ Time	Pulse/ PEFR	O$_2$ %Sat	BP	Intervention, Meds, Exam, Comments

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

Patient instructions:_____

Follow-up call to patient: Time_____ Comments:_____

Clinical impression: **True SR**   **Questionable SR**   **No 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 3. Anaphylaxis treatment record.

soning, hypoglycemia, and seizure disorder. Specific signs and symptoms of anaphylaxis might present singly in other disorders. Examples are urticaria-angioedema, hereditary angioedema, and asthma.

Annotation 5. Immediate intervention

The clinician should remember that anaphylaxis occurs as part of a continuum. Symptoms not immediately life-threatening might 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.

1. Assess airway, breathing, circulation, and level of consciousness (altered mentation might suggest the presence of hypoxia).
2. Administer epinephrine. Aqueous epinephrine 1:1000 dilution (1 mg/mL), 0.2 to 0.5 mL (0.01 mg/kg in children, maximum 0.3-mg dosage) in-

tramuscularly or subcutaneously every 5 minutes, as necessary, should be used to control symptoms and increase blood pressure. Consider dose-response effects. *Note:* 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 with subcutaneous injections in the thigh have not yet been done. Moreover, these studies were not performed in patients experiencing anaphylaxis. For this reason, the generalizability of these findings to the clinical setting of anaphylaxis has not been established. Although intuitively more rapid absorption and higher epinephrine levels would seem desirable, the clinical significance of this finding is not known. No data support the use of epinephrine in anaphylaxis through a nonparenteral route. However, alternative routes of administration have been anecdotally

___Flowsheet   ___Treatment Algorithm   ___BP cuff/monitor*   ___Stethoscope

AIRWAY   OXYGEN

__Disposable Facemask   __O$_2$ E-cylinder w/wrench; >1100 psi (>1/2 full)
__Infant   __Extension tubing
__Toddler   __Adult pocket mask with extension port
__Child/Small Adult   __Pediatric oxygen mask
__Adult   __Pediatric Ambubag
__Nasal Cannula (adult)
__Oropharyngeal airways
__6cm
__7cm
__8cm
__9cm
__10cm

MEDICATIONS   IV SUPPLIES

__Epinephrine 1:1000 1 ml ampules (3)   __0.9% normal saline (4 1000ml bags)
__Epinephrine 1:1000 multidose vial   __5% dextrose (1 250ml bag for admixture)
__Diphenhydramine (Benadryl) 50 mg/ml IV __Macrodrip admin. sets, 10-15 drops/ml
__Benadryl liquid 12.5 mg/5 ml   __Minidrip set, 60 drops/ml (for dopamine)
__Ranitidine (Zantac) 25 mg/ml IV   __Connection tubing
__Prednisone 10mg tablets   __Three-way stopcock
__Prednisolone syrup 15 mg/ml   __Catheter needles gauge 16,18,20,22
__Methylprednisolone (Solumedrol) 125mg vial __Butterfly needles gauge 19,21
__Glucagon 1mg/ml vial   __Syringes w/needles 1ml, 10ml, 20ml
__Atropine 0.5 mg/ml IV   __Tourniquet (2)—may substitute extra BP cuff
__Albuterol inhalation solution, 0.5%   __1" synthetic tape (e.g., Transpore^R)
__Dopamine 200 mg/5 ml (2 ampules)   __Latex-free gloves
                                          __Alcohol swabs (box)
                                          __IV Pole

*Sphygmomanometer/electronic BP monitoring device should be calibrated annually. A minimum of 3 cuff sizes should be available (child, adult, obese/large adult).

Replace supplies within one month of expiration date. Check supplies monthly and re-stock after use. Sphygmomanometer and oxygen tank connections should be checked weekly 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 4. Suggested anaphylaxis supply check sheet

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 emergency care that might be necessary depending on response to epinephrine

1. Place patient in the 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 and to the heart and kidneys.

2. Establish and maintain airway. Ventilatory assistance through a 1-way valve facemask with an oxygen inlet port (eg, Pocket-Mask [Laerdal®, Preparedness Industries, Ukiah, Calif] or similar device) might be necessary. Ambubags of less than 700 mL are discouraged in adults in the absence of an endotracheal tube because ventilated volume will not overcome 150 to 200 mL of anatomic dead space to provide effective tidal volume. (Ambubags can be used in children, provided the reservoir volume of the device is sufficient.) Endotracheal intubation or cricothyroidotomy might be considered where appropriate and provided that clinicians are adequately trained and proficient in this procedure.

3. Administer oxygen. Oxygen should be administered to patients with anaphylaxis who have prolonged reactions, have pre-existing hypoxemia or myocardial dysfunction, receive inhaled β-agonists as part of

therapy for anaphylaxis, or require multiple doses of epinephrine. Continuous pulse oximetry and/or arterial blood gas determination (where available) should guide oxygen therapy where hypoxemia is a concern.

4. Consider a normal saline intravenous line for fluid replacement and venous access. Lactated Ringer's solution might potentially contribute to metabolic acidosis, and dextrose is rapidly extravasated from the intravascular circulation to the interstitial tissues. Increased vascular permeability in anaphylaxis might permit transfer of 50% of the intravascular fluid into the extravascular space within 10 minutes. Crystalloid volumes (eg, saline) of up to 7 L might be necessary. One to 2 L of normal saline should be administered to adults at a rate of 5 to 10 mL/kg in the first 5 minutes. Patients with congestive heart failure or chronic renal disease should be observed cautiously to prevent volume overload. 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. Aqueous epinephrine 1:1000, 0.1 to 0.3 mL in 10 mL of normal saline, can be administered intravenously over several minutes and repeated as necessary in cases of anaphylaxis not responding to epinephrine injections and volume resuscitation. Alternatively, an epinephrine infusion can be prepared by adding 1 mg (1 mL) of a 1:1000 dilution of epinephrine to 250 mL of D5W to yield a concentration of 4.0 μg/mL. This solution is infused at a rate of 1 to 4 μg/min (15 to 60 drops per minute with a microdrop apparatus [60 drops per minute = 1 mL = 60 mL/h]), increasing to a maximum of 10.0 μg/min. If an infusion pump is available, an alternative 1:100,000 solution of epinephrine (1 mg [1 mL] in 100 mL of saline) can be prepared and administered intravenously at an initial rate of 30 to 100 mL/h (5-15 μg/min), titrated up or down depending on clinical response or epinephrine side effects (toxicity). A dosage of 0.01 mg/kg (0.1 mL/kg of a 1:10,000 solution; maximum dose, 0.3 mg) is recommended for children. Alternative pediatric dosage by the "rule of 6" is as follows: 0.6× body weight (in kilograms) = the number of milligrams diluted to a total of 100 mL of saline; then 1 mL/h delivers 0.1 μg/kg/min. *Note:* Because of the risk for potentially lethal arrhythmias, epinephrine should be administered intravenously only during cardiac arrest or to profoundly hypotensive patients who have failed to respond to intravenous volume replacement and several injected doses of epinephrine. In situations in which hemodynamic monitoring is available (eg, emergency department or intensive care facility), continuous hemodynamic monitoring is essential. However, use of intravenous epinephrine should not be precluded in a scenario in which such monitoring is unavailable if the clinician deems administration is essential after failure of several epinephrine injections. If intravenous epinephrine is considered essential under these special circumstances, monitoring by available means (eg, every-minute blood pressure and pulse measurements and electrocardiographic monitoring, if available) should be conducted.

5. Consider diphenhydramine, 1 to 2 mg/kg or 25 to 50 mg per dose (parenterally). *Note:* H_1 antihistamines are considered second-line therapy to epinephrine and should never be administered alone in the treatment of anaphylaxis.

6. Consider ranitidine, 50 mg in adults and 12.5 to 50 mg (1 mg/kg) in children, which might be diluted in 5% dextrose to a total volume of 20 mL and injected intravenously over 5 minutes. Cimetidine (4 mg/kg) can be administered intravenously to adults, but no pediatric dosage in anaphylaxis has been established. *Note:* 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 therapy to epinephrine.

7. Bronchospasm resistant to adequate doses of epinephrine: consider inhaled β-agonist (eg, nebulized albuterol, 2.5 to 5 mg in 3 mL of saline and repeat as necessary).

8. Hypotension refractory to volume replacement and epinephrine injections: consider vasopressor infusion. Continuous hemodynamic monitoring is essential. For example, dopamine (400 mg in 500 mL of 5% dextrose) can be infused at 2 to 20 μg/kg/min and titrated to maintain systolic blood pressure of greater than 90 mm Hg.

9. Consider glucagon infusion when concomitant β-adrenergic blocking agent complicates treatment. Glucagon dosage is 1 to 5 mg (20-30 μg/kg [maximum dose, 1 mg] in children) administered intravenously over 5 minutes and followed by an infusion (5 to 15 μg/min) titrated to clinical response.

10. Consider systemic glucocorticosteroids for patients with a history of idiopathic anaphylaxis or asthma and patients who experience severe or prolonged anaphylaxis. Glucocorticosteroids usually are not helpful acutely but potentially might prevent recurrent or protracted anaphylaxis. If given, intravenous glucocorticosteroids should be administered every 6 hours at a dosage equivalent to 1.0 to 2.0 mg/kg/d. Oral administration of glucocorticosteroids (eg, prednisone, 0.5 mg/kg) might be sufficient for less critical anaphylactic episodes.

11. Consider transportation to emergency department or intensive care facility.

Annotation 7. Cardiopulmonary arrest during anaphylaxis

1. Cardiopulmonary resuscitation and advanced cardiac life support measures.
2. High-dose epinephrine administered intravenously (ie, rapid progression to high dose). A common sequence

is 1 to 3 mg (1:10,000 dilution) slowly administered intravenously over 3 minutes, 3 to 5 mg administered intravenously over 3 minutes, and then a 4 to 10 μg/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 μg/min rate of infusion) repeated every 3 to 5 minutes for ongoing arrest. Higher subsequent dosages (0.1-0.2 mg/kg; 0.1 mL/kg of a 1:1,000 solution) might be considered for unresponsive asystole or pulseless electrical activity.

3. Rapid volume expansion.
4. Atropine and transcutaneous pacing if asystole and/or pulseless electrical activity are present.
5. Prolonged resuscitation is encouraged, if necessary, because efforts are more likely to be successful in anaphylaxis.
6. Transport to emergency department or intensive care facility, as setting dictates.

Annotation 8. Observation and subsequent follow-up

Observation periods must be individualized because there are no reliable predictors of biphasic or protracted anaphylaxis on the basis of initial clinical presentation. Follow-up accordingly must be individualized and based on such factors as clinical scenario and distance from the patient's home to the closest emergency facility. After resolution of the acute episode, patients should be provided with an epinephrine syringe and receive proper instruction for self-administration in case of a subsequent episode. In circumstances in which an allergist-immunologist is not already involved, it is strongly recommended that individuals who have experienced acute anaphylaxis should receive consultation from an allergist-immunologist regarding diagnosis, prevention, and treatment.

Annotation 9. Consider consultation with an allergist-immunologist

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

Consultation with an allergist-immunologist is recommended when:

1. the diagnosis is doubtful or incomplete;
2. the symptoms are recurrent or difficult to control;
3. help is needed in evaluation and management of medication use or side effects;
4. help is needed in medical management or adherence to treatment;
5. help is needed in the diagnosis or management of IgE-mediated reactions or identification of allergic triggers;
6. the patient is a candidate for desensitization (eg, penicillin) or immunotherapy (eg, venom-specific immunotherapy);
7. the patient requires daily medications for prevention;
8. the patient requires intensive education regarding avoidance or management;
9. help is needed with new or investigative therapy;
10. treatment goals have not been met;
11. anaphylaxis is complicated by one or more comorbid conditions or concomitant medications; or
12. the patient has requested a subspecialty consultation.

SUMMARY STATEMENTS

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

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 studies (eg, serum tryptase) is essential. **B**
4. In the management of a patient with a previous episode, education is necessary. Emphasis on early treatment, specifically the self-administration of epinephrine, is essential. **C**
5. The patient should be instructed to wear and/or carry identification denoting his or her condition (eg, Medic Alert jewelry). **C**

Management of anaphylaxis

6. Medical facilities should have an established protocol to deal with anaphylaxis and the appropriate equipment to treat the episode. In addition, telephone numbers for paramedical rescue squads and ambulance services might be helpful to have on hand. **B**
7. 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**
8. Anaphylactic (IgE-dependent) and anaphylactoid (IgE-independent) reactions differ mechanistically, but the clinical presentations are identical. **C**
9. The more rapidly anaphylaxis develops, the more likely the reaction is to be severe and potentially life-threatening. **C**
10. Prompt recognition of signs and symptoms of anaphylaxis is crucial. If there is any doubt, it is generally better to administer epinephrine. **C**
11. Any health care facility should have a plan of action for anaphylaxis should it occur. Physicians and office staff should maintain clinical proficiency in anaphylaxis management. **D**
12. 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. **A/D**

13. 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**

Anaphylaxis to foods

14. Severe food reactions have been reported to involve the gastrointestinal, cutaneous, respiratory, and cardiovascular systems. **D**

15. The greatest number of anaphylactic episodes in children has involved peanuts, tree nuts (ie, walnuts, pecans, and others), fish, shellfish, milk, and eggs **(C)**. The greatest number of anaphylactic episodes in adults is due to shellfish **(C)**. Clinical cross-reactivity with other foods in the same group is unpredictable **(B)**. Additives can also cause anaphylaxis **(C)**.

16. Anaphylactic reactions to foods almost always occur immediately. Symptoms might then subside, only to recur several hours later. **A**

17. The most useful diagnostic tests include skin tests and food challenges. *In vitro* testing with foods might be appropriate as an alternative screening procedure. **C**

18. Double- or single-blind placebo-controlled food challenges can be done in patients with suspected food allergy in a medical facility by personnel experienced in performing the procedure and prepared to treat anaphylaxis. **B**

19. Patient education should include discussion about avoidance and management of accidental ingestion. **C**

20. Schools might present a special hazard for the student with food allergy. Epinephrine should be available for use by the individuals in the school trained to respond to such a medical emergency. **C**

Latex-induced anaphylaxis

21. Latex (rubber) hypersensitivity is a significant medical problem, and 3 groups are at higher risk of reaction: health care workers, children with spina bifida and genitourinary abnormalities, and workers with occupational exposure to latex. **B**

22. Skin prick tests with latex extracts should be considered for patients who are members of high-risk groups or who have a clinical history of possible latex allergy to identify IgE-mediated sensitivity. Although a standardized, commercial skin test reagent for latex is not available in the United States, many allergy centers have prepared latex extracts from gloves to be used for clinical testing. It should be noted, however, that such extracts prepared from gloves demonstrate tremendous variability in content of latex antigen. *In vitro* assays for IgE to latex might also be useful, although these tests are generally less sensitive than skin tests. **C**

23. Patients with spina bifida (regardless of a history of latex allergy) and other patients with a positive history of latex allergy ideally should have all medical-surgical-dental procedures performed in a latex-safe environment and as the first case of the day. **D**

24. A latex-safe environment is an environment in which no latex gloves are used in the room or surgical suite and no latex accessories (catheters, adhesives, tourniquets, and anesthesia equipment) come into contact with the patient. **D**

25. In health care settings general use of latex gloves with negligible allergen content, powder-free latex gloves, and nonlatex gloves and medical articles should be considered in an effort to minimize exposure to latex allergen. Such a combined approach might minimize latex sensitization of health care workers and patients and should reduce the risk of inadvertent reactions to latex in previously sensitized individuals. **C**

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

26. 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, flushing, and/or edema of the skin. **C**

27. It might be difficult to differentiate between immune and nonimmune mast cell–mediated reactions and pharmacologic effects from the variety of medications administered during general anesthesia. **B**

28. Thiopental allergy has been documented by using skin tests. **B**

29. Neuromuscular blocking agents, such as succinylcholine, can cause nonimmunologic histamine release, but there have been reports of IgE-mediated mechanisms in some cases. **B**

30. Reactions to opioid analgesics are usually caused by direct mast cell–mediator release rather than IgE-dependent mechanisms. **B**

31. Antibiotics that are administered perioperatively can cause immunologic or nonimmunologic generalized reactions. **B**

32. Protamine can also cause severe systemic reactions through IgE-mediated or nonimmunologic mechanisms. **B**

33. Latex is a potent allergen, and IgE-mediated reactions to latex during anesthesia have been clearly documented. Patients with multiple surgical procedures (eg, patients with spina bifida) and health care workers are at greater risk of latex sensitization. Precautions for latex-sensitive patients include avoiding the use of latex gloves and latex blood pressure cuffs, as well as latex intravenous tubing ports and rubber stoppers from medication vials. **B**

34. Blood transfusions can elicit a variety of systemic reactions, some of which might be IgE mediated or mediated through other immunologic mechanisms. **B**

35. Methylmethacrylate (bone cement) has been associated with hypotension and various systemic reactions, although no IgE mechanism has yet been documented. **C**
36. The evaluation of IgE-mediated reactions to medications used during anesthesia can include skin testing to a variety of anesthetic agents. **B**
37. The management of anaphylactic or anaphylactoid reactions that occur during general anesthesia is similar to the management of anaphylaxis in other situations. **B**

Seminal fluid-induced anaphylaxis

38. Anaphylaxis caused by human seminal fluid has been shown to be due to IgE-mediated sensitization by proteins of varying molecular weights. **B**
39. Localized seminal plasma hypersensitivity has been well described and is likely IgE mediated on the basis of successful response to rapid seminal plasma desensitization. **C**
40. History of atopic disease is the most consistent risk factor. However, anecdotal case reports have been associated with gynecologic surgery, injection of anti-RH immunoglobulin, and the postpartum state. **C**
41. The diagnosis is confirmed by means of skin and/or *in vitro* tests for serum-specific IgE by using proper reagents obtained from fractionation of seminal fluid components. **C**
42. Prevention of reactions to seminal fluid can be accomplished by barrier use of condoms. **C**
43. Immunotherapy to properly fractionated seminal fluid proteins has been universally successful in preventing anaphylaxis to seminal fluid, provided the sensitizing seminal fluid fractions are used as immunogens. Successful intravaginal graded challenge with unfractionated seminal fluid has been reported in a few cases, but the duration of protection is unknown. **C**
44. Localized and/or systemic seminal plasma hypersensitivity is not associated with infertility. **D**

Exercise-induced anaphylaxis

45. Exercise-induced anaphylaxis is a form of physical allergy. Premonitory symptoms can include diffuse warmth, itching, and erythema. Urticaria generally ensues, with progression to confluence and often angioedema. Episodes can progress to include gastrointestinal symptoms, laryngeal edema, and/or vascular collapse. **B**
46. Factors that have been associated with exercise-induced anaphylaxis include medications (eg, aspirin and other nonsteroidal anti-inflammatory drugs) or food ingestion before and after exercise. **C**
47. Patients with exercise-induced anaphylaxis might have a higher incidence of personal and/or family history of atopy. **C**
48. Medications used prophylactically are not useful in preventing exercise-induced anaphylaxis. **C**

49. If exercise-induced anaphylactic episodes have been associated with the ingestion of food, exercise should be avoided in the immediate postprandial period. **C**
50. Patients with exercise-induced anaphylaxis should carry epinephrine and should wear and/or carry Medic Alert identification denoting their condition. They should have a companion with them when exercising. This companion should be versed in the use of an EpiPen. **D**

Idiopathic anaphylaxis

51. The symptoms of idiopathic anaphylaxis are identical to those of episodes related to known causes. **C**
52. Patients with idiopathic anaphylaxis should receive an intensive evaluation, including a meticulous history to rule out a definite cause of the events. **C**
53. There might be a need for specific laboratory studies to exclude systemic disorders, such as systemic mastocytosis. This might include a serum tryptase level when the patient is asymptomatic, a ratio of β-tryptase to total tryptase during an event, and selective allergy skin testing. **C**

Anaphylaxis and allergen immunotherapy vaccines

54. There is a small risk of near-fatal and fatal anaphylactic reactions to allergen immunotherapy injections. **C**
55. Patients with asthma, particularly poorly controlled asthma, are at higher risk for serious systemic reactions to allergen immunotherapy injections (**C**). Patients taking β- adrenergic blocking agents are at higher risk for serious systemic reactions to allergen immunotherapy injections (**B**).
56. 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

57. Low-molecular-weight medications induce an IgE-mediated reaction only after combining with a carrier protein to produce a complete multivalent antigen. **B**
58. Penicillin is the most common cause of drug-induced anaphylaxis. **C**
59. Penicillin spontaneously degrades to major and minor antigenic determinants, and skin testing with reagents on the basis of these determinants yields negative results in about 90% of patients with a history of penicillin allergy. **B**
60. The negative predictive value of penicillin skin testing (for immediate-type reactions) is between 97% and 99% (depending on the reagents used), and the positive predictive value is at least 50%. **B**

61. The extent of allergic cross-reactivity between penicillin and cephalosporins is unknown but appears to be low. Four percent of patients proved to have penicillin allergy by means of penicillin skin testing react to cephalosporin challenges. **C**

62. Patients with a history of penicillin allergy who have negative penicillin skin test responses might safely receive cephalosporins. **B**

63. Patients with a history of penicillin allergy who have positive penicillin skin test responses might (1) receive an alternate (non–β-lactam) antibiotic, (2) receive a cephalosporin through graded challenge, or (3) receive a cephalosporin through rapid desensitization. **F**

64. Aztreonam does not cross-react with other β-lactams, except ceftazidime, with which it shares a common R-group side chain. **B**

65. Carbapenems should be considered cross-reactive with penicillin. **C**

66. 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**

67. Aspirin and nonsteroidal anti-inflammatory drugs are the second most common cause of drug-induced anaphylaxis. **C**

68. Anaphylactic reactions to aspirin and nonsteroidal anti-inflammatory drugs appear to be medication specific and do not cross-react with structurally unrelated aspirin or other nonsteroidal anti-inflammatory drugs. **D**

Prevention of anaphylaxis

69. Major risk factors related to anaphylaxis include, but are not limited to, prior history of such reactions, concomitant β-adrenergic blocker therapy, exposure, or atopic background. Atopic background might be a risk factor for venom- and latex-induced anaphylaxis and possibly anaphylactoid reactions to radiographic contrast material but not for anaphylactic reactions to medications.

70. Avoidance measures are successful if future exposure to drugs, foods, additives, or occupational allergens can be prevented. Avoidance of stinging and biting insects is also possible in many cases. Prevention of systemic reactions during allergen immunotherapy is dependent on the specific circumstances involved.

71. 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.

72. Pharmacologic prophylaxis should be used to prevent recurrent anaphylactoid reactions to radiographic contrast material, fluorescein, as well as to prevent idiopathic anaphylaxis. Prophylaxis with glucocorticosteroids and antihistamines markedly reduces the occurrence of subsequent reactions.

TABLE I. Frequency of occurrence of signs and symptoms of anaphylaxis*†

Signs and symptoms	
Cutaneous	90%
Urticaria and angioedema	85%-90%
Flushing	45%-55%
Pruritus without rash	2%-5%
Respiratory	40%-60%
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.

73. Allergen immunotherapy with the appropriate stinging insect venom should be recommended for patients with systemic sensitivity to stinging insects because this treatment is highly (90% to 98%) effective.

74. Desensitization to medications that are known to have caused anaphylaxis can be effective. In most cases the effect of desensitization is temporary, and if the medication is required some time in the future, the desensitization process must be repeated.

75. Patient education might be the most important preventive strategy. Patients should be carefully instructed about hidden allergens, cross-reactions to various allergens, 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.

EVALUATION AND MANAGEMENT OF THE PATIENT WITH A HISTORY OF EPISODES 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 studies (eg, serum tryptase is essential). **B**

4. In the management of a patient with a previous episode, education is necessary. Emphasis on early treatment, specifically the self-administration of epinephrine, is essential. **C**

TABLE II. Types of anaphylaxis and the differential diagnosis of anaphylaxis and anaphylactoid reactions

Types of anaphylaxis and anaphylactoid reactions
  Anaphylaxis (anaphylactoid reactions) to exogenous agents
  Anaphylaxis and anaphylactoid reactions to physical factors
    Exercise
    Cold
    Heat
    Sunlight
  Idiopathic anaphylaxis
Anaphylaxis and anaphylactoid reactions caused by the excess
    endogenous production of histamine
  Systemic mastocytosis
  Urticaria pigmentosa
  Basophilic leukemia
  Acute promyelocytic leukemia with tretinoin treatment
  Hydatid cyst
Vasodepressor (vasovagal) reactions
Other forms of shock
  Hemorrhagic
  Hypoglycemic
  Cardiogenic
  Endotoxic
Flushing syndromes
  Carcinoid
  Red man syndrome caused by 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
Nonorganic diseases
  Panic attacks
  Vocal cord dysfunction syndrome
Miscellaneous
  C1 esterase deficiency syndromes (acquired and hereditary
    angioedema)
  Pheochromocytoma
  Neurologic (seizure, stroke)
  Capillary leak syndrome

5. The patient should be instructed to wear and/or carry identification denoting his or her condition (eg, Medic Alert jewelry). **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.[1-14] A summary of the signs and symptoms as reported in these series, totaling 1865 patients, is seen in Table I. These series include patients with exercise-induced anaphylaxis, patients with idiopathic anaphylaxis, patients of all age ranges, and reviews of patients with anaphylaxis from various causes. The most frequent manifestations of anaphylaxis are cutaneous, occurring in more than 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.[15,16] Friends and/or family members present during the event should be interviewed to better assess the signs and symptoms of the reaction. Anaphylaxis can present with unusual manifestations (eg, syncope without any other sign or symptom).[17,18]

The history and the record should include the time(s) of the occurrence of the attack(s), any treatment required during the attack(s), and the duration of the episode(s). A detailed history of all potential causes should be obtained. This includes a list of ingestants consumed before the event, including both foods and drugs; any possible stings or bites occurring before the event; whether the event occurred during exercise; location of the event (eg, work versus home); and whether the event was related to exposure to heat or cold or sexual activity. The patient's atopic status should be noted because food-induced and idiopathic anaphylaxis are more common in atopic than nonatopic individuals. Also, in women the history should include any relationship between the attack(s) and their menstrual cycle. Return of symptoms after a remission should be noted because this might indicate a late-phase reaction,[6] which might require a prolonged period of observation if subsequent events occur.

Differential diagnosis

The vast majority of patients presenting with a history consistent with anaphylaxis will have experienced an anaphylactic event. Nonetheless, it is important not to immediately accept this diagnosis. The differential diagnosis must be considered when the history is taken, even in patients with a previous history of anaphylaxis. Comprehensive differential diagnoses are seen in Table II.

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, and pruritus) and the presence of bradycardia during the vasodepressor reaction instead of the tachycardia usually seen with anaphylaxis. However, it should be noted that bradycardia can occur during anaphylaxis as well.[19] 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.

Flushing episodes can mimic anaphylactic events. As noted, the history should include all of the drugs that the

patient was taking before the event. Several drugs and ingestants, including niacin, nicotine, catecholamines, angiotensin-converting enzyme inhibitors, and alcohol, can induce flushing.[20] Other conditions that cause flushing must be considered, including gastrointestinal and thyroid tumors, the carcinoid syndrome, pheochromocytoma, hyperglycemia, postmenopausal flush, alcohol-induced flushing, and the red man syndrome caused by the administration of vancomycin. Laboratory analysis (see below) can be helpful in establishing the cause of flushing.

There are a group of postprandial syndromes that can mimic anaphylaxis, such as monosodium glutamate–induced reaction and reactions to scombroid fish (see "Food allergy: a practice parameter"). The latter is increasing in frequency,[21] and because it is caused by 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 can be more of a flush (sunburn-like) than urticaria. Symptoms might affect more than one individual if others also ingested the fish causing the reaction and serum tryptase levels are normal.

Nonorganic disease, such as vocal cord dysfunction and panic attacks, should be considered in the differential diagnosis.

Laboratory studies

Laboratory studies to be considered are shown in Table III. Serum tryptase and plasma and urinary histamine metabolites might be helpful in establishing the diagnosis of anaphylaxis.[22,23] Plasma histamine levels begin to increase within 5 to 10 minutes of the onset of symptoms of anaphylaxis and remain increased for 30 to 60 minutes.[24,25] Therefore they are not of help if the patient is seen as long as an hour or more after the onset of the event.[24] However, urinary methyl-histamine levels are increased for a longer duration of time.[26] Serum tryptase levels peak 1 to 1½ hours after the onset of anaphylaxis and can persist for as long as 5 hours after the onset of symptoms.[25] The best time to measure serum tryptase levels is between 1 to 2 hours but no longer than 6 hours after the onset of symptoms.[25] The best time to measure plasma histamine levels is between 10 minutes and 1 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 increase of only one of these mediators.[25]

There are 2 forms of tryptase, α and β.[22] α-Tryptase is secreted constitutively, and β-tryptase is released only during degranulation episodes. This observation is useful in distinguishing between systemic anaphylaxis per se and a degranulation of mast cells related to mastocytosis. The distinction between these 2 disorders rests on the fact that patients with mastocytosis, because of their increased mast cell burden, constitutively produce larger amounts of α-tryptase (compared with normal subjects), whereas patients who have true anaphylactic events of other causes

TABLE III. 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 hours. Ideally, the measurement should be obtained between 1 and 2 hours after the initiation of symptoms.
Plasma histamine	Plasma histamine levels begin to increase within 5-10 min and remain increased 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-h Urinary histamine metabolite (methyl histamine)	Urinary histamine and its metabolites are increased for a longer period of time, up to 24 hours.
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 (VIP), 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.

will have normal baseline levels of α-tryptase. During anaphylactic events, β-tryptase is secreted in large amounts in both groups. Therefore the ratio of total tryptase (α plus β) to β-tryptase can be useful in distinguishing degranulation episodes in patients with mastocytosis from anaphylactic events in patients without this disorder. In addition, constitutively increased levels of α-tryptase are helpful in making a diagnosis of mastocytosis. A ratio of total tryptase (α plus β) to β-tryptase of 10 or less is indicative of an anaphylactic episode not related to systemic mastocytosis, whereas a ratio of 20 or greater is consistent with systemic mastocytosis.[22] This distinction is made possible because of the fact that the immunoassay for tryptase using a B12 mAb or a G4 mAb recognizes both α- and β-tryptase, whereas an assay using a G5 mAb recognizes only β-tryptase.[22]

It has been proposed that an increase of postmortem serum tryptase level be used to establish anaphylaxis as a cause of death.[27] However, it should be clearly noted that postmortem increase of serum tryptase concentrations is not a specific finding and therefore cannot be considered diagnostic of an anaphylactic death. There are reports detailing nonanaphylactic deaths exhibiting increased

postmortem serum tryptase levels.[28-30] Thus the presence of an increased postmortem tryptase level cannot be considered pathognomonic for a death caused by anaphylaxis or an anaphylactoid event. Neither can an absence of an increased serum tryptase level postmortem be considered sufficient to rule out anaphylaxis or an anaphylactoid event as the cause of death.[28]

In search of the culprit in patients with possible anaphylaxis to food, leftover or vomited food might be useful as a source of antigen for the creation of a custom RAST reagent.[27]

In the management of a patient with a previous episode, education is necessary, including emphasis on early treatment, specifically the self-administration of epinephrine. Patients who have experienced an episode of anaphylaxis should also be equipped with identification denoting their possible susceptibility to future episodes. This can consist of a card and/or identification jewelry (eg, Medic Alert).

Medical facilities should have an established protocol to deal with anaphylactic episodes and the appropriate equipment to treat the episode. In addition, telephone numbers for paramedical rescue squads and ambulance services should be on hand.

MANAGEMENT OF ANAPHYLAXIS

Summary Statements

6. Medical facilities should have an established protocol to deal with anaphylaxis and the appropriate equipment to treat the episode. In addition, telephone numbers for paramedical rescue squads and ambulance services might be helpful to have on hand. **B**

7. 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**

8. Anaphylactic (IgE-dependent) and anaphylactoid (IgE-independent) reactions differ mechanistically, but the clinical presentations are identical. **C**

9. The more rapidly anaphylaxis develops, the more likely the reaction is to be severe and potentially life-threatening. **C**

10. Prompt recognition of signs and symptoms of anaphylaxis is crucial. If there is any doubt, it is generally better to administer epinephrine. **C**

11. Any health care facility should have a plan of action for anaphylaxis should it occur. Physicians and office staff should maintain clinical proficiency in anaphylaxis management. **D**

12. 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. **A/D**

13. 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**

Signs and symptoms of anaphylaxis

There is no universally accepted clinical definition of anaphylaxis.[31,32] Anaphylaxis is an acute life-threatening reaction that results from the sudden systemic release of mast cells and basophil mediators. It has varied clinical presentations, but respiratory compromise and cardiovascular collapse cause the most concern because they are the most frequent causes of anaphylactic fatalities.[32] Anaphylactic (IgE-dependent) and anaphylactoid (IgE-independent) reactions differ mechanistically, but the clinical presentations are identical. Anaphylaxis might affect the level of consciousness (impairment might reflect hypoxia), the upper and lower airways (dysphonia, stridor, cough, wheezing, or shortness of breath), the 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, or diarrhea). In addition, some patients might have symptoms of lightheadedness, headache, uterine cramps, feeling of impending doom, or unconsciousness.

Urticaria and angioedema are the most common manifestations of anaphylaxis[2,8,33] and often occur as the initial signs of severe anaphylaxis. However, cutaneous findings might be delayed or absent in rapidly progressive anaphylaxis. The more rapidly anaphylaxis develops, the more likely the reaction is to be severe and potentially life-threatening. Moreover, symptoms not immediately life-threatening might progress rapidly unless treated promptly and appropriately.

Anaphylaxis often produces signs and symptoms within seconds to minutes of exposure to an offending stimulus, but some reactions might develop later (eg, greater than 30 minutes after exposure). Late-phase or biphasic reactions, which occur 8 to 12 hours after the initial attack, have also been reported.[34-36] Some protracted reactions can last up to 32 hours, despite aggressive treatment.[35,36]

Increased vascular permeability, a characteristic feature of anaphylaxis, allows transfer of 50% of the intravascular fluid into the extravascular space within 10 minutes.[37,38] As a result, hemodynamic collapse can occur rapidly, with little or no cutaneous or respiratory manifestations.[15,16]

Differential diagnosis in anaphylaxis

The differential diagnosis of anaphylaxis is reviewed elsewhere in this parameter (see ''Evaluation and management of the patient with a history of episodes of anaphylaxis'' and Table II). Like anaphylaxis, several conditions can cause abrupt and dramatic patient collapse. Among conditions to consider are vasodepressor (vasovagal) reactions, acute anxiety (eg, panic attack or hyperventilation syndrome), myocardial dysfunction, pulmonary embolism, systemic mast cell disorders, foreign-body aspiration, acute poisoning, hypoglycemia, and seizure disorder. Specific signs and symptoms of

anaphylaxis can present singly in other disorders. Examples are urticaria-angioedema, hereditary angioedema, and asthma.

The vasodepressor (vasovagal) reaction probably is the condition most commonly confused with anaphylactic and anaphylactoid 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 usually normal or increased, and the skin is typically cool and pale. Tachycardia is the rule in anaphylaxis, but it might be absent in patients with conduction defects, patients with increased vagal tone caused by a cardioinhibitory (Bezold-Jarisch) reflex, or patients who take sympatholytic medications.

It should be recognized that urticaria and angioedema might be part of the continuum of anaphylaxis but in isolation are not anaphylaxis.

Management of anaphylaxis

The management of anaphylactic and anaphylactoid reactions is identical. A sequential approach to management is outlined in Table I, and a sample treatment flow sheet is presented in Fig 1. The following equipment supplies should be available for the treatment of anaphylaxis in medical settings in which allergen immunotherapy is administered or in which other medications or biologic agents are administered by means of injection[39,40]: (1) stethoscope and sphygmomanometer; (2) tourniquets, syringes, hypodermic needles, and large-bore needles (14-gauge needles); (3) injectable aqueous epinephrine 1:1000; (4) equipment for administering oxygen; (5) equipment for administering intravenous fluids; (6) oral airway; (7) diphenhydramine or similar injectable antihistamine; (8) corticosteroids for intravenous injection; and (9) a vasopressor (eg, dopamine or norepinephrine). Glucagon, an automatic defibrillator, and a 1-way valve facemask with an oxygen inlet port (eg, Pocket-Mask or similar device) are other materials that some clinicians might find desirable, depending on the clinical setting.

Fig 2 provides a sample checklist to track supplies needed to treat anaphylaxis and expiration dates for medications-fluids. Not all items need to be present in each office.

Evaluation and treatment in a latex-safe environment is optimal for patients with concomitant latex allergy. It is important to stress that these steps are subject to physician discretion and that variations in sequence and performance rely on physician judgment. Additionally, when a patient should be transferred to an emergency facility depends on the skill, experience, and clinical decision making of the individual physician. Medical offices in which anaphylaxis is likely to occur (eg, in which allergen immunotherapy is administered) should consider periodic anaphylaxis practice drills tailored to local emergency medical service capabilities and response times. Essential ingredients to such drills are identification of a person who will be responsible for calling emergency medical services and a person who will document treatment and time each

is rendered. The emergency kit should be up to date and complete. Everyone who will be directly involved in patient care should, for example, easily be able to locate necessary supplies and rapidly assemble fluids for intravenous administration.

Assessment and maintenance of airway, breathing, and circulation are necessary before proceeding to other management steps. Measurement of peak expiratory flow rate and pulse oximetry might be useful in patients with dyspnea, bronchospasm, or both. Epinephrine administration and the maintenance of adequate oxygenation and intravascular volume have high priority.

Epinephrine. Epinephrine is the treatment of choice for acute anaphylaxis.[31,41,42] Aqueous epinephrine 1:1000 dilution, 0.2 to 0.5 mL (0.01 mg/kg in children; maximum dose, 0.3 mg) administered intramuscularly or subcutaneously every 5 minutes, as necessary, should be used to control symptoms and increase blood pressure. Consider dose-response effects. *Note:* If the clinician deems it appropriate, the 5-minute interval between injections can be liberalized to permit more frequent injections.

Subsequent therapeutic interventions depend on the severity of the reaction and the initial response to epinephrine. No data support the use of epinephrine in anaphylaxis through a nonparenteral route. However, alternative routes of administration have been anecdotally successful. These include, for example, inhaled epinephrine in the presence of laryngeal edema or sublingual injection 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.[43]

Fatalities during anaphylaxis usually result from delayed administration of epinephrine and from severe respiratory complications, cardiovascular complications, or both. There is no absolute contraindication to epinephrine administration in anaphylaxis.[44,45]

Absorption is more rapid and plasma levels are higher in children not experiencing anaphylaxis who receive epinephrine intramuscularly in the thigh with an autoinjector.[46] Intramuscular injection into the thigh (vastus lateralis) in adults not experiencing anaphylaxis is also superior to intramuscular or subcutaneous injection into the arm (deltoid), neither of which achieves increased plasma epinephrine levels compared with endogenous levels.[47] Spring-loaded (eg, EpiPen) automatic epinephrine devices administered intramuscularly and intramuscular epinephrine injections through a syringe into the thigh in adults not experiencing anaphylaxis provide dose-equivalent plasma levels.[46,47] However, similar studies comparing intramuscular injections to subcutaneous injections in the thigh have not yet been done.

The UK consensus panel on emergency guidelines and the international consensus guidelines for emergency cardiovascular care both recommend intramuscular epinephrine injections for anaphylaxis.[31,41] Both publications also propose that epinephrine can be repeated every 5 minutes, as clinically needed, in both adults and children.[31,41] It seems reasonable to infer that the 5-minute

interval between injections can be liberalized to permit more frequent injections if the clinician deems it appropriate. Development of toxicity or inadequate response to epinephrine injections indicates that additional therapeutic modalities are necessary.

No established dosage or regimen for intravenous epinephrine in anaphylaxis is recognized. Inferences can be drawn from the emergency cardiac care consensus guidelines for intravenous epinephrine for adults and children.[41,48] An epinephrine infusion might be prepared by adding 1 mg (1 ml) of a 1:1000 dilution of epinephrine to 250 mL of D5W to yield a concentration of 4.0 μg/ml. This 1:250,000 solution is infused at a rate of 1 to 4 μg/min (15-60 drops per minute with a microdrop apparatus [60 drops per minute = 1 mL = 60 mL/h]), increasing to a maximum of 10.0 μg/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 μg/min; maximum dose, 0.3 mg) is recommended for children. Alternative pediatric dosage by the ''rule of 6'' is as follows: 0.6 × body weight (in kilograms) = numbers of milligrams diluted to total 100 mL of saline; then 1 mL/h delivers 0.1 μg/kg/min.[48] (See Table II for infusion guidelines in children.)

An alternative epinephrine infusion protocol has been suggested for adults with anaphylaxis. Brown and colleagues conducted a prospective, randomized, double-blind, placebo-controlled, crossover study of *Myrmecia pilosula* (jack jumper ant) venom immunotherapy in which 21 otherwise healthy adults experienced systemic reactions after diagnostic sting challenge.[19] Two individuals experienced urticarial reactions and received no epinephrine. The remaining 19 patients (8 of whom had systolic blood pressure of less than 90 mm Hg) received a 1:100,000 solution of epinephrine (1 mg [1 mL] in 100 mL of saline) intravenously by means of infusion pump at an initial rate of 30 to 100 mL/h (5-15 μg/min) titrated up or down depending on clinical response or epinephrine side effects (toxicity). This infusion was discontinued 30 minutes after resolution of all signs and symptoms of anaphylaxis.

Five of the 8 patients with hypotension also received a 1-L bolus of normal saline during the first few minutes of treatment. Eighteen of the 19 patients who received epinephrine infusions had symptomatic improvement and systolic blood pressures of greater than 90 mm Hg within 5 minutes. The remaining individual required an additional 2 L of saline (3 L total).

Note: Because of the risk for potentially lethal arrhythmias, epinephrine should be administered intravenously only during cardiac arrest or to profoundly hypotensive subjects who have failed to respond to intravenous volume replacement and several injected doses of epinephrine. In situations in which hemodynamic monitoring is available (eg, emergency department or intensive care facility), continuous hemodynamic monitoring is essential.[32] However, use of intravenous epinephrine should not be precluded in a scenario in which such monitoring is not available if the clinician deems its administration is essential after failure of several epinephrine injections in the thigh. If intravenous epinephrine is considered essential under these special circumstances, monitoring by available means (eg, every-minute blood pressure and pulse measurements and electrocardiographic monitoring) should be conducted.

H_1 and H_2 antagonists. Antihistamines (H_1 and H_2 antagonists) are supportive in the treatment of anaphylaxis. However, these agents have a much slower onset of action than epinephrine and should never be administered alone as treatment for anaphylaxis. Thus antihistamine use in anaphylaxis should be considered second-line treatment after the administration of epinephrine.

However, antihistamines are useful in the treatment of urticaria-angioedema or pruritus when they appear as manifestations of the anaphylactic episode. Diphenhydramine, 25 to 50 mg for adults and 1 mg/kg (up to 50 mg) for children, slowly might be administered intravenously. Oral diphenhydramine, in identical dosages, might be sufficient for milder attacks.

The role of H_2 antagonists, such as ranitidine and cimetidine, is more controversial, but several reports have demonstrated that a treatment with a combination of H_1 and H_2 antagonists is more effective in anaphylaxis than treatment with H_1 antagonists alone.[49-56] For example, an emergency department–based study involving 91 adult patients demonstrated that a combination of diphenhydramine and ranitidine provided superior resolution of cutaneous symptoms and tachycardia compared with diphenhydramine and saline.[55]

No controlled studies support use of one H_2 antagonist over another. Most studies have used either cimetidine or ranitidine. Ranitidine might be the drug of choice because it has fewer potential drug interactions. The recommended administration for ranitidine is 1 mg/kg in adults and 12.5 to 50 mg in children infused over 10 to 15 minutes.[57] Ranitidine also can be diluted in 5% dextrose to a total volume of 20 mL and injected over 5 minutes. Cimetidine, 4 mg/kg in adults, should be administered slowly because rapid intravenous administration might produce hypotension.[58] Cimetidine should not be administered to children with anaphylaxis because no dosages have been established.

Corticosteroids. Systemic corticosteroids have no role in the acute management of anaphylaxis because they might have no effect for 4 to 6 hours, even when administered intravenously. Although corticosteroids traditionally have been used in the management of anaphylaxis, their effect has never been evaluated in placebo-controlled trials. However, if their effects on other allergic diseases, such as asthma, are extrapolated, corticosteroids might potentially prevent protracted or biphasic anaphylaxis. They also form an essential part of the preventive management of frequent idiopathic anaphylaxis.[59] Corticosteroids administered during anaphylaxis might provide additional benefit for patients with asthma or other conditions recently treated with corticosteroids.[45]

If given, intravenous corticosteroids should be administered early in the treatment of anaphylaxis at a dosage equivalent to 1.0 to 2.0 mg/kg/d of methylprednisolone

every 6 hours. Oral administration of prednisone, 0.5 mg/kg, might be sufficient for milder attacks.

Oxygen and adrenergic agonists. Oxygen should be administered to patients with anaphylaxis who have prolonged reactions, have pre-existing hypoxemia or myocardial dysfunction, receive inhaled β_2-agonists, or require multiple doses of epinephrine. Arterial blood gas determination (where available) or continuous pulse oximetry should guide oxygen therapy where hypoxemia is a concern. Inhaled β_2-agonists, such as albuterol (0.5 mL or 2.5 mg of a 5% solution), might be administered for bronchospasm refractory to epinephrine.

Persistent hypotension–potential contributory factors and appropriate roles of volume replacement and vasopressors. Numerous cases of unusually severe or refractory anaphylaxis have been reported in patients receiving β-adrenergic blockers.[36,60-72] 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.[73,74] That β-blockade can influence the severity of anaphylaxis is supported by evidence from both human and animal studies.[73-78] Greater severity of anaphylaxis observed in patients receiving β-blockers might relate, in part, to a blunted response to epinephrine commonly administered to treat anaphylaxis.[73] Epinephrine might paradoxically worsen anaphylaxis through facilitating unopposed α-adrenergic and reflex vagotonic effects. In patients receiving β-blockers, increased propensity not only for bronchospasm but also decreased cardiac contractility with perpetuation of hypotension and bradycardia might exist.[78-80] For these reasons, β-blocker–related anaphylaxis might be more likely to be refractory to management. Evidence suggests that more serious anaphylaxis might also be promoted in the setting of β-blocker exposure because of the action of β-blockers on cyclic nucleotides, which can lead to heightened mediator release.[73,78] There are no epidemiologic studies that indicate that anaphylaxis occurs more frequently in patients receiving β-blockers. The observed risk for more serious anaphylaxis in patients receiving β-blockers has promoted caution regarding casual use of β-blockers in patients who might or will be exposed to an anaphylactogenic stimulus, including but not limited to (1) patients receiving allergen immunotherapy or undergoing immediate hypersensitivity skin testing,[81,82] (2) patients receiving infusion of radiographic contrast media,[75] and (3) patients with anaphylactic potential to hymenoptera venom.[64,73] Suspension of β-blocker treatment in such patients might be appropriate; however, in view of β-blocker withdrawal syndromes observed in selected cases and the clear benefits that will accrue from use of β-blockers in patients for whom these drugs are indicated,[63-65,83-85] this determination must be considered carefully from an individualized risk-benefit standpoint.

The contention that increased risk for more severe anaphylaxis with β-blockers also includes cardioselective agents is supported by reports of unusually severe anaphylaxis described in association with β_1-selective antagonists[60-64] and *in vitro* histamine release demonstrated with either β_1- or β_2-antagonists.[65,66] Systemic effects, including potential for bronchospasm and bradycardia, are well described with use of ophthalmic β-blockers.[86] For the above reasons, until more data are available, absence of greater risk for anaphylaxis with β-blocker exposure in patients receiving cardioselective or ophthalmic β-blockers cannot be assumed.

In summary, patients taking β-adrenergic antagonists might 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 can inhibit the β-adrenergic receptor.

Epinephrine administered during anaphylaxis to patients taking β-adrenergic antagonists might be ineffective. In this situation both glucagon administration and isotonic volume expansion (in some circumstances up to 7 L of crystalloid are necessary) might be necessary.[72,87-89] Glucagon might reverse refractory bronchospasm and hypotension during anaphylaxis in patients receiving β-adrenergic antagonists by activating adenyl cyclase directly and bypassing the β-adrenergic receptor.[90] The recommended dosage for glucagon is 1 to 5 mg (20-30 μg/kg [maximum dose, 1 mg] in children) administered intravenously over 5 minutes and followed by an infusion (5-15 μg/min) titrated to clinical response. Protection of the airway is important because glucagon might cause emesis and risk aspiration in severely drowsy or obtunded patients. Placement in the lateral recumbent position might be sufficient airway protection for many of these patients.

Fluid resuscitation. Changes in vascular permeability during anaphylaxis might permit transfer of 50% of the intravascular fluid into the extravascular space within 10 minutes.[37,38] This effective shift of blood volume is countered by compensatory vasopressor mechanisms that involve the release of norepinephrine and epinephrine,[91] as well as activation of the angiotensin system.[92,93] Resulting increases in catecholamines might produce varied effects. Some patients during anaphylaxis experience abnormal increases in peripheral resistance (reflecting maximal vasoconstriction),[94] whereas others have decreased systemic vascular resistance, despite increased endogenous catecholamine levels.[91] These variable effects of internal compensatory mechanisms might explain why epinephrine injections sometimes fail to help in anaphylaxis. In contrast, these patients might respond to fluid replacement. (See Table IV for age-dependent criteria for hypotension, as defined by international consensus guidelines for pediatric advanced life support.)

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 (eg, anaphylactic shock) because it stays in the intravascular space longer than dextrose and

TABLE IV. Special considerations for anaphylaxis in children[22]

A. 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

B. 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) = no. of mg diluted to total 100 mL of saline; then 1 mL/h delivers 1 μg/kg/min
Epinephrine	0.1 μg/kg/min	0.6× body weight (in kg) = no. of mg diluted to total 100 mL of 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 diluted or more concentrated drug solution on the basis of a standard drug concentration, in which case an individual dose must be calculated for each patient and each infusion rate as follows: $Infusion\ rate(mL/h) = (Weight[kg] \times Dose[\mu g/kg/min] \times 60\ min/h)/Concentration(\mu g/mL)$.

contains no lactate, which might potentially exacerbate metabolic acidosis. One to 2 L of normal saline might need to be administered to adults at a rate of 5 to 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.[19] Large volumes are often required, but it might be appropriate to monitor patients with underlying congestive heart failure or chronic renal disease for signs of volume overload once the effective fluid deficit is replaced.

Vasopressors. Vasopressors, such as dopamine (400 mg in 500 mL of 5% dextrose), administered at 2 to 20 μg/kg/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. (See Table II for pediatric dosing of dopamine.) Dopamine will frequently increase blood pressure while maintaining or enhancing blood flow to the renal and splanchnic circulation. A critical care specialist might need to be consulted for any patient with intractable hypotension.[95] These agents would not be expected to work as well in those patients who have experienced maximal vasoconstriction as their internal compensatory response to anaphylaxis.

After promising results in various animal models for cardiopulmonary resuscitation, vasopressin has been investigated for potential benefit in human cardiac arrest in 3 randomized controlled trials,[96-98] and one case report investigated its effects on hypotension in 2 adults who experienced insect sting anaphylaxis.[99] Wenzel et al[98] proposed that "vasopressin was superior to epinephrine in patients with asystole" on the basis of post hoc statistical analysis (1 of 29 statistical comparisons), did not correct statistically for multiple comparisons, and included no sensitivity analysis for 33 subjects excluded from analy-

sis.[100] The other 2 randomized controlled trials concluded there were no significant differences in survival to discharge or neurologic function when vasopressin was compared with epinephrine in cardiac arrest.

In summary, high-quality randomized control trials performed to date have not demonstrated that vasopressin efficacy equals or exceeds that of epinephrine in clinical outcomes of treatment for cardiac arrest. No controlled studies have been performed to evaluate the potential efficacy of vasopressin alone in anaphylaxis or in combination with epinephrine.

Analysis of anaphylaxis outcomes and procedures

After treatment for any episode of acute anaphylaxis, the clinician should consider an analysis of event and possible precipitating cause, particularly with respect to those steps that could or should be done to prevent future episodes. (See "Anaphylaxis and immunotherapy" on prevention of anaphylaxis and specific scenario of anaphylaxis.) The clinical staff should also critique its approach to the management of anaphylaxis after each episode in regard to what worked well and what needs improvement.

Guide to physician-supervised management of anaphylaxis

I. Immediate intervention
   a. Assessment of airway, breathing, circulation, and adequacy of mentation
   b. Administer aqueous epinephrine 1:1000 dilution, 0.2 to 0.5 mL (0.01 mg/kg in children, max 0.3 mg dosage) intramuscularly or subcutaneously into the arm (deltoid) every 5 minutes, as necessary, to control symptoms and blood pressure. The arm permits easy access for administration of epinephrine, although intramuscular injection into the anterolateral thigh (vastus lateralis) produces higher and more rapid peak plasma levels compared with injections administered intramuscularly or subcutaneously in the arm. Similar studies comparing intramuscular injections with subcutaneous injections in the thigh have not yet been done. Although intuitively higher and more rapid peak plasma levels seen with intramuscular injection in the thigh would appear desirable, the clinical significance of these data is not known. Alternatively, an epinephrine autoinjector (eg, EpiPen [0.3 mg] or EpiPen Jr [0.15 mg]) might be administered through clothing into the lateral thigh. Repeat every 5 minutes as necessary (avoid toxicity). *Note:* Some guidelines suggest that the 5-minute interval between injections can be liberalized to permit more frequent injections if the clinician deems it appropriate. There is no absolute contraindication to epinephrine administration in anaphylaxis. However, several anaphylaxis fatalities have been attributed to injudicious use of intravenous epinephrine.

II. Subsequent measures that might be necessary depending on response to epinephrine
   a. Place patient in recumbent position and elevate lower extremities.
   b. Establish and maintain airway (endotracheal tube or cricothyrotomy can be performed if required and if clinicians are adequately trained and proficient).
   c. Administer oxygen at 6-8 L/min.
   d. Establish venous access.
   e. Use normal intravenous saline for fluid replacement. Might require large volumes of crystalloid (1-2 L of normal saline to adults can be administered at 5-10 mL/kg in first 5 minutes; children can receive up to 30 mL/kg in the first hour). If hypotension persists, rapid infusion of volume expanders (colloid-containing solutions) might be necessary.

III. Where appropriate, specific measures to consider after epinephrine injections
   a. An epinephrine infusion might 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 μg/mL. This solution is infused intravenously at a rate of 1 to 4 μg/min (15 to 60 drops per minute with a microdrop apparatus [60 drops per minute = 1 mL = 60 mL/h]), increasing to a maximum of 10.0 μg/min for adults and adolescents. If an infusion pump is available, an alternative 1:100,000 solution of epinephrine (1 mg [1 mL] in 100 mL saline) can be prepared and administered intravenously at an initial rate of 30 to 100 mL/h (5-15 μg/min), titrated up or down depending on clinical response or epinephrine side effects (toxicity). A dosage of 0.01 mg/kg (0.1 mL/kg of a 1:10,000 solution; maximum dose, 0.3 mg) is recommended for children. Alternative pediatric dosage by the "rule of 6" is as follows: 0.6 $\times$ body weight (in kilograms) = number of milligrams diluted to total 100 mL of saline; then 1 mL/h delivers 0.1 μg/kg/min. *Note:* Because of the risk for potentially lethal arrhythmias, epinephrine should be administered intravenously only during cardiac arrest or to profoundly hypotensive subjects who have failed to respond to intravenous volume replacement and several injected doses of epinephrine. In situations in which hemodynamic monitoring is available (eg, emergency department or intensive care facility), continuous hemodynamic monitoring is essential. However, use of intravenous epinephrine should not be precluded in a scenario in which such monitoring is not available if the clinician deems its administration is essential after failure of several epinephrine injections in the thigh. If intravenous epinephrine is considered essential under these special circumstances, monitoring by available means (eg, every-minute blood pressure and pulse measurements and electrocar-

diographic monitoring, if available) should be conducted.
   b. Diphenhydramine, 1-2 mg/kg or 25-50 mg/dose (parenterally).
   c. Consider ranitidine, 1 mg/kg, which can be diluted in 5% dextrose (D5W) to a total volume of 20 mL and injected intravenously over 5 minutes. Cimetidine (4 mg/kg) can be administered intravenously to adults, but no pediatric dosage in anaphylaxis has been established. *Note:* In the management of anaphylaxis, a combination of diphenhydramine and ranitidine is superior to diphenhydramine alone.
   d. For bronchospasm resistant to epinephrine, use nebulized albuterol, 2.5-5 mg in 3 mL of saline, and repeat as necessary.
   e. For hypotension refractory to volume replacement and epinephrine injections, dopamine, 400 mg in 500 mL D5W, can be administered intravenously at 2 to 20 μg/kg/min, with the rate titrated to maintain adequate blood pressure. Continuous hemodynamic monitoring is essential.
   f. Where β-blocker therapy complicates treatment, consider glucagon, 1-5 mg (20-30 μg/kg [maximum, 1 mg] in children), administered intravenously over 5 minutes followed by an infusion (5-15 μg/min). Aspiration precautions should be observed because glucagon can cause nausea and emesis.
   g. Consider systemic glucocorticosteroids for patients with a history of idiopathic anaphylaxis and asthma and patients who experience severe or prolonged anaphylaxis. Glucocorticosteroids usually are not helpful acutely, but potentially might prevent recurrent or protracted anaphylaxis. If given, intravenous steroids should be administered every 6 hours at a dosage equivalent to methylprednisolone (1.0-2.0 mg/kg/day). Oral administration of prednisone, 0.5 mg/kg, might be sufficient for less critical anaphylactic episodes.
   h. Consider transportation to the emergency department or an intensive care facility.

IV. Key additional interventions for cardiopulmonary arrest occurring during anaphylaxis
   a. Cardiopulmonary resuscitation and advanced cardiac life support measures.
   b. High-dose intravenous epinephrine (ie, rapid progression to high dose). A commonly used sequence is 1 to 3 mg (1:10,000 dilution) slowly administered intravenously over 3 minutes, 3 to 5 mg administered intravenously over 3 minutes, and then a 4 to 10 μg/min infusion. The recommended initial resuscitation dosage in children is 0.01 mg/kg (0.1 mL/kg of a 1:10,000 solution up to a maximum of 0.3 mg) repeated every 3 to 5 minutes for ongoing arrest. Another option is to start an epinephrine infusion and deliver up to 10 μg/min. Higher subsequent dosages (0.1-0.2

mg/kg; 0.1 ml/kg of a 1:1,000 solution) might be considered for unresponsive asystole or pulseless electrical activity. These arrhythmias are often observed during cardiopulmonary arrest that occurs in anaphylaxis.

c. Rapid volume expansion is mandatory.

d. Atropine and transcutaneous pacing should be considered if asystole and/or pulseless electrical activity are present.

e. Prolonged resuscitation efforts are encouraged, if necessary, because efforts are more likely to be successful in anaphylaxis when the patient is young and has a healthy cardiovascular system.

f. Transport to the emergency department or an intensive care facility, as the setting dictates.

VI. Observation and subsequent follow-up

a. Observation periods must be individualized because there are no reliable predictors of biphasic or protracted anaphylaxis on the basis of initial clinical presentation. Follow-up accordingly must be individualized and based on such factors as clinical scenario and distance from the patient's home to the closest emergency facility. After resolution of the acute episode, patients should be provided with an epinephrine syringe and receive proper instruction for self-administration in case of a subsequent episode. All individuals experiencing anaphylaxis require a careful history and targeted diagnostic evaluation in consultation with an allergist-immunologist.

ANAPHYLAXIS TO FOODS
Summary Statements

14. Severe food reactions have been reported to involve the gastrointestinal, cutaneous, respiratory, and cardiovascular systems. **D**

15. The greatest number of anaphylactic episodes in children has involved peanuts, tree nuts (ie, walnuts, pecans, and others), fish, shellfish, milk, and eggs **(C)**. The greatest number of anaphylactic episodes in adults is due to shellfish **(C)**. Clinical cross-reactivity with other foods in the same group is unpredictable **(B)**. Additives can also cause anaphylaxis **(C)**.

16. Anaphylactic reactions to foods almost always occur immediately. Symptoms might then subside only to recur several hours later. **A**

17. The most useful diagnostic tests include skin tests and food challenges. *In vitro* testing with foods might be appropriate as an alternative screening procedure. **C**

18. Double- or single-blind placebo-controlled food challenges can be done in patients with suspected food allergy in a medical facility by personnel experienced in performing the procedure and prepared to treat anaphylaxis. **B**

19. Patient education should include discussion about avoidance and management of accidental ingestion. **C**

20. Schools might present a special hazard for the student with food allergy. Epinephrine should be available for use by the individuals in the school trained to respond to such a medical emergency. **C**

The true incidence of fatal or near-fatal anaphylaxis to food is unknown. One estimate, about a thousand severe episodes per year, has been extrapolated from emergency department reporting.[101] In 3 recent surveys food allergy was reported to be the most commonly identified cause of anaphylaxis, accounting for 35% to 55% of cases.[2,3,102]

Severe adverse food reactions can involve several major systems. Respiratory manifestations might include oral and pharyngeal swelling, hoarseness and laryngeal edema, wheezing, cough, breathlessness, and/or chest tightness. Cardiovascular manifestations might include cardiac ischemia, arrhythmias, and hypotension, which might produce loss of consciousness. Gastrointestinal signs and symptoms include nausea, bloating, diarrhea, and severe abdominal pain. It should be noted that in some female subjects, abdominal pain involves the lowest portion of the abdomen and might be due to uterine contractions. Cutaneous manifestations have included urticaria, angioedema, and erythema. Angioedema and erythema can occur without urticaria. Angioedema of the eyelids and involvement of the conjunctiva is possible. Individuals might also experience a metallic taste and a sense of impending doom.

Etiology

Many foods have been reported to cause anaphylaxis.[103,104] The greatest number of anaphylactic reactions to foods in the United States have been reported after exposure to peanuts, tree nuts, milk, and eggs in children, and shellfish, peanuts, and fish in adults.[105-108]

It should not be assumed that a reaction to one member of a food family necessarily incriminates any or all other members.[109-111] Certain foods contain epitopes that cross-react immunologically (eg, peanut and soy) but might not cross-react in terms of the clinical response.[112]

History

Obtaining a thorough history from patients who have experienced a life-threatening reaction that might have been caused by a food is crucial. The history might be unequivocal, as in the individual who eats a single food (eg, peanut) and shortly thereafter has anaphylaxis. It should be remembered that highly sensitive patients might experience anaphylaxis after inhalation (eg, cooking fish) exposure. However, in many patients with anaphylaxis, a food offender cannot be immediately identified. If anaphylaxis occurs repeatedly and food allergy is suspected, it might be possible to assemble a list of ingredients from foods associated with these events by searching for common constituents.[104]

The time from ingestion to symptom onset in food allergy is typically rapid, usually within minutes, but might be delayed up to an hour and in some instances up to a few hours.[111,113] Symptoms might then subside only to recur several hours later (biphasic reaction).

Fatal food anaphylaxis might begin with mild symptoms, sometimes involving the skin, and then progress to shock with cardiovascular collapse over a 1- to 3-hour period.[107]

In evaluating suspected food allergy, it is important to consider associated factors, such as exercise after food ingestion (see section on exercise-induced anaphylaxis and "Food allergy: a practice parameter").[13]

Diagnostic testing

Presently, the most useful diagnostic tests for food allergy include skin tests, *in vitro* serum specific IgE assays, and oral food challenges. The test of choice is the skin test. It should be recognized that although many food allergens have been well characterized, standardized food extracts are not currently available, and skin tests might need to be performed to fresh food extracts.[103] If skin testing is done, the challenge solution should be diluted, and testing should be performed by a physician experienced in the procedure in a setting with appropriate rescue equipment and medications available. In certain instances *in vitro* serum specific IgE determinations can be helpful.

Food challenges

The degree to which the history and diagnostic testing confirm that a single specific food is responsible for the reaction that the patient has experienced will determine the need for a food challenge. If the history and diagnostic testing give an unequivocal answer, no challenge is necessary. Inadvertent ingestion of a food will often confirm that the initial suspicion about that food was correct.

However, if a definite food has not been identified as the cause of the reaction but foods are still suspected, food challenge might be necessary because identification of the food might be life-saving.[107] Double- or single-blind placebo-controlled food challenges can be performed safely in individuals with a history of food-induced anaphylaxis.[104-108] Open and nonblinded challenge can also be performed. It might be especially helpful when it is unlikely that the suspect food was responsible for the reaction and the patient needs to be reassured that it is safe to ingest the particular agent used. However, it might be necessary to begin with a minute amount of the suspected food, and the challenge should be stopped when the first symptoms occur. Often, but not always, pruritus of the oral tissues or nausea is the initial complaint after challenge with the suspected food. It is important to remember that even a small amount of food allergen can precipitate anaphylaxis.[103]

Patient education

Education regarding avoidance and management of accidental ingestion of foods known to produce anaphy-laxis is crucial because neither presently available medications nor immunotherapy has been shown to consistently prevent such reactions, and epinephrine has not always been effective in reversing anaphylaxis. In addition to attempting to identify the food that is causing anaphylaxis, it is important to teach patients about situations in which accidental ingestion might occur.[114-116]

Patients with food hypersensitivity should be taught to effectively read and interpret labels on foods and to inquire about ingredients in restaurant meals. In addition, patients should be educated about foods that might cross-react with the identified offender (eg, various shellfish). There are educational materials available from dietitians, as well as organizations such as the Food Allergy Network (10400 Eaton Place, #107, Fairfax, VA 22030-2208; phone, 703-691-3179; fax, 703-691-2713). Fortunately, the food industry is becoming more responsive about labeling of food allergens and providing information to the public about accidental contamination of food products with known allergens.

Exposure to foods at school, daycare, camps, and restaurants constitutes a special hazard for individuals with food allergy. If a child has a history of severe reactions to foods, the foods that caused the reaction should be identified for school personnel. School personnel should be informed about a student's history of anaphylaxis and the specific food (or foods) to which the child is allergic. An allergen-free environment should be constructed for the child at mealtime to prevent inadvertent ingestion such as might occur with shared food. There should be a written response plan available that can be initiated immediately if a reaction occurs. Unfortunately, not all school policy allows children to have ready access to epinephrine at school. However, youngsters allergic to foods are covered by the Americans with Disabilities Act, which should make it easier to arrange an emergency medical response for accidental severe food reactions. Individuals with a history of a life-threatening reaction to a food should carry epinephrine. This includes individuals who have had any respiratory symptoms or a decrease in blood pressure during a reaction to a food. Patients at risk should carry identification, such as a Medic Alert jewelry.

If epinephrine is prescribed for the patient, the patient must understand that it should be available at all times. This instruction might require constant reinforcement. Compliance is more likely in young children, for whom adults are responsible. Compliance is the most difficult in adolescents and young adults. If a reaction is of such severity that epinephrine is required, the patient should be transported to the nearest emergency facility by ambulance for monitoring after epinephrine has been administered.

Ongoing evaluation

It is recommended that patients be instructed in the importance of reporting any and all anaphylactic reactions to their physician as soon as possible after they occur. If the exact cause of these reactions has not been identified, discussing the reaction with the physician while it is still

fresh in the patient's mind might help to define the specific food causing the reaction. If the cause of the patient's reactions is known, this interaction can re-establish that the food responsible for these reactions was correctly identified and that the appropriate treatment response was initiated.

LATEX-INDUCED ANAPHYLAXIS

Summary Statements

21. Latex (rubber) hypersensitivity is a significant medical problem, and 3 groups are at higher risk of reaction: health care workers, children with spina bifida and genitourinary abnormalities, and workers with occupational exposure to latex. **B**
22. Skin prick tests with latex extracts should be considered for patients who are members of high-risk groups or who have a clinical history of possible latex allergy to identify IgE-mediated sensitivity. Although a standardized commercial skin test reagent for latex is not available in the United States, many allergy centers have prepared latex extracts from gloves to be used for clinical testing. It should be noted, however, that such extracts, prepared from gloves, demonstrate tremendous variability in the content of latex antigen. *In vitro* assays for IgE to latex might also be useful, although these tests are generally less sensitive than skin tests. **C**
23. Patients with spina bifida (regardless of a history of latex allergy) and other patients with a positive history of latex allergy ideally should have all medical-surgical-dental procedures performed in a latex-safe environment and as the first case of the day. **D**
24. A latex-free environment is an environment in which no latex gloves are used in the room or surgical suite and no latex accessories (catheters, adhesives, tourniquets, and anesthesia equipment) come into contact with the patient. **D**
25. In health care settings general use of latex gloves with negligible allergen content, powder-free latex gloves, and nonlatex gloves and medical articles should be considered in an effort to minimize exposure to latex allergen. Such a combined approach might minimize latex allergen. Such a combined approach might minimize latex sensitization of health care workers and patients and should reduce the risk of inadvertent reactions to latex in previously sensitized individuals. **C**

Latex sensitization caused by IgE mast cell–mediated reactivity to any or a number of antigens from *Hevea brasiliensis*, the source of latex, occurs in a significant percentage of the health care worker population,[117] up to 75% of the spina bifida population,[118,119] and in the population undergoing multiple surgical procedures. Sporadic cases of latex-induced anaphylaxis have been reported because of hair glue and plastic balls with latex pits.[120,121] An incidence of up to 6.5% of the general population has been noted to have detectable IgE to latex.[122] Atopic and latex-exposed individuals are also at higher risk of latex sensitization. Individuals might be sensitized to minor or major antigens. No more than 240 separate polypeptides can be discerned by means of 2-dimensional electrophoresis of latex cap. Less than 25% of these react with IgE from patients with latex allergy. These tend to cluster into groups of 11 proteins.[123] With exposure, sensitized individuals might experience urticaria, angioedema, rhinitis, bronchospasm, and anaphylaxis.

Incidence

Latex-induced anaphylaxis can present in the operating room in patients, surgeons, nurses, or anesthesiologists. Latex has been reported to account for up to 17% of cases of intraoperative anaphylaxis.[123]

Clinical findings

The features of intraoperative anaphylaxis from latex might differ considerably from latex-induced anaphylaxis not associated with surgical procedures. Although cutaneous, hypotensive, and respiratory events occur in both, hypotensive cardiovascular collapse is a feature of surgical reactions, and dizziness or syncope might be found largely in anaphylaxis induced by nonsurgical procedures.[124] In some situations anaphylaxis might not be IgE mediated, such as those caused by radiocontrast media, but it has become clear that latex-induced anaphylaxis is due to IgE mast cell–mediated mechanisms. Thus after a careful history and physical examination, detection of IgE to latex is quite helpful in the diagnosis. Unfortunately, no commercially available skin test reagent is available in the United States. For this reason, other materials, such as latex glove extracts, are often used. It should be noted that such extracts are not standardized, and the amount of latex allergen within these extracts is highly variable. Latex ELISA or CAP are also available, but because of the variability in the antigen response, the *in vitro* tests have highly variable sensitivity and specificity characteristics. The sensitivity has been found to be as low as 50% to as high as 100%.[125,126]

Latex-induced anaphylaxis might occur in a variety of situations, all involving direct contact with latex devices, usually gloves, or instruments or with aerosolization of latex antigen adhered to the cornstarch donning powder of latex gloves. Thus latex-induced reactions can occur with operative procedures when gloves are donned. Latex-induced reactions might occur immediately with latex contact or might be delayed from 30 to 60 minutes. Intraoperative latex-induced anaphylaxis might be related to the administration of drug through a latex port before surgery or during the surgical procedure itself. Latex-induced reactions have also been reported to occur during dental procedures from latex glove or dams, during obstetric or gynecologic examinations, during latex condom use, and from blowing into rubber balloons. Patients with spina bifida are potentially at risk at each surgical procedure because of the numbers of procedures they undergo.

Treatment

Latex-induced anaphylaxis is an IgE mast cell–mediated reaction and should be treated as any other case of anaphylaxis (see section on management of anaphylaxis, beginning on page S500).

Prevention

As aerosolization, inhalation, or direct contact with latex devices or latex antigen is the event resulting in the allergic response, and avoidance is clearly the prime mode of therapy. For the sensitive health care worker, latex gloves should not be worn, and the worker's colleagues should wear nonpowdered latex or nonlatex gloves. The workplace should be latex safe, with all nonglove latex devices replaced by nonlatex devices. A latex-free emergency cart (Table V) should be available to treat reactions. Although it is unclear whether rubber stopper vials can cause anaphylaxis, they should be avoided.

Latex precautions should be instituted when a latex-sensitive patient undergoes a surgical procedure, an obstetric or gynecologic examination, or dental care. The surgical room, dental area, or examination area should be free of latex devices. No latex gloves should be used, and the patient should be the first case of the day. Appropriate emergency medications must be available for treatment should a reaction occur. With these measures, latex-induced anaphylaxis should be markedly reduced.

It is important to recognize that cross-reactivity between latex and foods can occur. The commonly reported cross-reactive foods include banana, avocado, kiwi, and chestnut (see "Food allergy: a practice parameter").

ANAPHYLAXIS DURING GENERAL ANESTHESIA, THE INTRAOPERATIVE PERIOD, AND THE POSTOPERATIVE PERIOD

Summary Statements

26. 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, flushing, and/or edema of the skin. **C**
27. It might be difficult to differentiate between immune and nonimmune mast cell–mediated reactions and pharmacologic effects from the variety of medications administered during general anesthesia. **B**
28. Thiopental allergy has been documented with skin tests. **B**
29. Neuromuscular blocking agents, such as succinylcholine, can cause nonimmunologic histamine release, but there have been reports of IgE-mediated mechanisms in some cases. **B**
30. Reactions to opioid analgesics are usually caused by direct mast cell–mediator release rather than IgE-dependent mechanisms. **B**
31. Antibiotics that are administered perioperatively can cause immunologic or nonimmunologic generalized reactions. **B**

TABLE V. 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
Webril tourniquets

32. Protamine can also cause severe systemic reactions through IgE-mediated or nonimmunologic mechanisms. **B**
33. Latex is a potent allergen, and IgE-mediated reactions to latex during anesthesia have been clearly documented. Patients with multiple surgical procedures (eg, patients with spina bifida) and health care workers are at greater risk of latex sensitization. Precautions for latex-sensitive patients include avoiding the use of latex gloves and latex blood pressure cuffs, as well as latex intravenous tubing ports and rubber stoppers from medication vials. **B**
34. Blood transfusions can elicit a variety of systemic reactions, some of which might be IgE mediated or mediated through other immunologic mechanisms. **B**
35. Methylmethacrylate (bone cement) has been associated with hypotension and various systemic reactions, although no IgE mechanism has yet been documented. **C**
36. The evaluation of IgE-mediated reactions to medications used during anesthesia can include skin testing to a variety of anesthetic agents. **B**
37. The management of anaphylactic or anaphylactoid reactions that occur during general anesthesia is similar to the management of anaphylaxis in other situations. **B**

Anaphylaxis or anaphylactoid reactions occur in 1:5000 to 1:25,000 general anesthetic administrations.[1] The mortality from anaphylaxis related to anesthesia is estimated to be as high as 6%. The multiple physiologic changes occurring before and during general anesthesia might limit or delay recognition of anaphylaxis. Signs of anaphylaxis include flushing or urticaria, hypotension, difficulty with intubation caused by laryngeal edema or increased ventilatory pressure, or inability to ventilate because of bronchospasm. Serum tryptase quantification during or immediately after a presumed anaphylactic or anaphylactoid event might be helpful in confirming clinical suspicion, particularly if a postevent sample demonstrates a decrease to normal value after the event.[1]

The causes of anaphylaxis or anaphylactoid reactions related to anesthesia are listed in order of approximate frequency of occurrence.[127-129]

- Muscle relaxants
- Latex
- Antibiotics, particularly β-lactam antibiotics
- Induction agents or hypnotics
- Opioids
- Colloids, particularly dextran, mannitol, or hydroxyethyl starch
- Blood products
- Others, including protamine, isosulfan blue dye for lymph node dissection, gelatin solution used for hemostasis, chlorhexidine, ethylene oxide, radiocontrast media, streptokinase, methylmethacrylate, chymopapain[130-133]

The rank order of occurrence is based on reviews for anesthesia during general surgery, but specific surgical procedures might differ with respect to likely cause.[127,128] For example, in cardiovascular surgery anesthesia-induced anaphylaxis is more likely caused by cephalosporins, gelatin solution, or protamine allergy rather than muscle relaxants.

Muscle relaxants are responsible for more than 60% of reactions during general anesthesia.[127,128,134,135] Most reactions occur because of direct mast cell activation, but life-threatening reactions are usually caused by specific IgE.[127,128] The shared tertiary or quaternary ammonium group results in cross-reactions among the muscle relaxants.[127,129] Succinylcholine might be more likely to cause reactions caused by flexibility of the molecule facilitating the cross-linking of specific IgE on mast cell or basophil membranes. Skin testing to specific dilutions of muscle relaxants has been useful in determining the safest agent after a suspected reaction.[136]

Natural rubber latex sensitivity is the second most common cause of perioperative anaphylaxis in some series. The incidence might be decreasing with time. Anaphylaxis caused by latex is more likely to be delayed or occur later during the procedure compared with that caused by muscle relaxants or induction agents. Multiple prior surgical procedures are a risk factor. A US Food and Drug Administration–approved *in vitro* test for latex-specific IgE is available, although false-negative results occur. A standardized skin-testing reagent is not available in the United States but is in Canada. Latex precautions are indicated if latex sensitivity is confirmed or highly suspected. Ideally, latex-safe operative suites should be available. If this is not an option, scheduling the anesthesia and procedure as the first case of the day and avoiding the use of latex products is suggested. Premedication regimens, usually including corticosteroids and combinations of antihistamines, might lessen the severity but have not been shown to prevent anaphylactic reactions.

Hypnotic induction agents are the third most likely cause of anesthesia anaphylaxis. Intravenous barbiturates have most commonly been responsible, but the reaction rate is probably less than 1:25,000, with the reported occurrence reflecting the common use of barbiturates. Mixing intravenous barbiturates with neuromuscular blocking agents in the same intravenous line might increase the likelihood of reactions. Skin testing has been reported with thioamyl and thiopental at 0.01 and 0.2 mg/mL, respectively.[137] Propofol is a nonbarbiturate induction agent and is useful if sensitivity to barbiturates is suspected. Specific IgE to propofol occurs, but most propofol reactions are due to direct mast cell activation.[138]

Narcotics used in anesthesia commonly cause flushing and urticaria after intravenous administration. The risk of anaphylaxis or anaphylactoid reactions, in contrast, is very rare.[139] Reducing the rate of opioid administration usually limits the severity of these reactions. Fentanyl does not directly stimulate histamine release through the mast cell opioid receptor.

Antibiotics are frequently administered before, during, or immediately after anesthesia and surgery. The most commonly implicated antibiotics resulting in reactions are β-lactams or vancomycin. IgE-mediated reactions occur in 0.04% to 0.015% of penicillin-treated subjects, and anaphylaxis occurs in approximately 0.001%. Intravenous administration of penicillin results in the most severe forms of anaphylaxis. Penicillin skin testing is useful to identify specific IgE. The sensitivity of penicillin skin testing is approximately 97% if aqueous penicillin and penicillin major determinant (Pre-pen) are used. The lack of a commercially available minor determinant, sensitivity to which can be associated with severe reactions, is an impediment. Percutaneous, followed by intracutaneous, testing with concentrations of up to 3 mg/mL for aqueous penicillin and 6×10^{-5} molar for major determinant are recommended to exclude penicillin allergy. *In vitro* testing for the major determinant is also available, but its negative predictive value is less well established and is less compared with immediate hypersensitivity testing.[140] Skin testing with penicillin derivatives or cephalosporins is not as well studied. Maximum testing concentrations of 1 to 3 mg/mL have been suggested for these other β-lactams. Carbapenems do not cross-react immunologically with penicillin. Desensitization schedules are available to facilitate use of β-lactam antibiotics, if absolutely necessary, in subjects with documented or suspected allergy. Vancomycin is a glycopeptide antibiotic selectively used for treatment of resistant organisms and for individuals with penicillin allergy. Administration, particularly rapid administration, might result in life-threatening anaphylactoid reactions. Evidence for both direct histamine release and direct myocardial depression partially explains this phenomenon. These nonimmunologic reactions to vancomycin can be reduced or eliminated by administration of a dilute solution, dissolved in at least 200 mL, that is slowly infused. Anaphylactic reactions to vancomycin occur but are much less common than anaphylactoid reactions. Skin testing with a concentration of up to 0.15 mg/mL has been reported, but the reliability of this testing is less secure than with penicillin. Skin testing might be of some value in distinguishing rate-related anaphylactoid reactions from anaphylaxis.

Intravenous protamine used to reverse heparin anti-coagulation might cause anaphylactic or anaphylactoid reactions. The latter reactions are characterized by an increase in pulmonary blood pressure. Proposed causes include both immunologic and nonimmunologic mechanisms. A case-control study showed that prior neutral protamine Hagedorn insulin use (odds ratio, 8.18 [2.08,32.2]), fish allergy (odds ratio, 24.5 [1.24,482.3]), and other medication allergy (odds ratio, 2.97 [1.25,7.07]) are independent risk factors.[141] Estimates are that up to 39% of patients undergoing cardiopulmonary bypass have one or more of these risk factors. Alternative agents might be used for heparin reversal, but these are not readily available. Pretreatment regimens with corticosteroids and antihistamines have been recommended, but no studies confirm efficacy.

Dextran and hydroxyethel starch (HES), large-molecular-weight polysaccharides, might be used as a nonblood product and for high oncotic fluid replacement during surgery. These agents are rarely associated with adverse reactions, probably anaphylactoid, because of complement activation. Estimates of reaction rates are 0.008% to 0.08% for dextran and 0.08% for HES. Specific antibodies can be detected for dextran and HES, but the clinical significance of these is unknown. Confirmation of dextran or HES as the cause of an adverse reaction is limited by the absence of accurate serologic or skin tests. Skin test reactivity to undiluted solutions has been described but again is of unknown significance.[142]

Case reports are also in the literature describing systemic reactions to albumin. Details are not available as to the mechanism of the adverse effects.

The ideal of preventing perianesthetic reactions is elusive because of the rare occurrence of reactions; the multiple pathophysiologic mechanisms, many of which are undefined; and the limited ability to test for risk or sensitization.[143] A careful medical history focusing on prior adverse reactions is most important. Any prior medication reactions nonspecifically increase the possibility of adverse reactions, and multiple previous medication reactions are a greater risk. Atopic subjects might be at heightened risk, either because of increased occurrence of reactions or, more often, increased severity of reactions. Asthma should be stabilized with lung function maximized and bronchial hyperreactivity minimized, if possible. β-Blocker therapy is a risk factor that ideally should be avoided. Previous anesthetic associated reactions should be evaluated thoroughly with specific testing if indicated. IgA-deficient subjects should receive washed red blood cells and no whole blood to avoid exposure to exogenous IgA. Intraoperative antibiotic administration should be at a slow rate with careful hemodynamic monitoring. Drugs with histamine-releasing properties, for example morphine, d-tubocurarine, vancomycin, or quaternary muscle relaxants, should be administered as slowly as possible, particularly in subjects with asthma or cardiopulmonary disease. Risk factors for latex hypersensitivity should be reviewed and consideration given to testing for specific IgE if any risk factors are identified.

Pretreatment regimens, as used for radiocontrast anaphylactoid reactions, have not been proved to prevent perianesthetic reactions but might reduce the severity of such reactions.

Local anesthetics

Adverse effects from local anesthetics are not uncommon, but immunologic mediated reactions after parenteral administration are very unusual. The usual cause of a local anesthetic reaction is a vasovagal response, anxiety, toxic complications, or an idiosyncratic reaction. Toxic effects usually result from inadvertent, systemic, high-dose administration. Systemic toxicity includes central nervous system stimulation or suppression and cardiac suppression with peripheral vasodilation. Epinephrine mixed with local anesthetics might contribute to the sensation of anxiety if systemic absorption occurs. IgE-mediated reactions to local anesthetics are exceedingly rare.[144]

SEMINAL FLUID–INDUCED ANAPHYLAXIS
Summary Statements

38. Anaphylaxis caused by human seminal fluid has been shown to be due to IgE-mediated sensitization by proteins of varying molecular weight. **B**
39. Localized seminal plasma hypersensitivity has been well described and is likely IgE mediated on the basis of successful response to rapid seminal plasma desensitization. **C**
40. History of atopic disease is the most consistent risk factor. However, anecdotal case reports have been associated with gynecologic surgery, injection of anti-RH immunoglobulin, and the postpartum state. **C**
41. The diagnosis is confirmed by means of skin and/or *in vitro* tests for serum-specific IgE by using proper reagents obtained from fractionation of seminal fluid components. **C**
42. Prevention of reactions to seminal fluid can be accomplished by barrier use of condoms. **C**
43. Immunotherapy to properly fractionated seminal fluid proteins has been universally successful in preventing anaphylaxis to seminal fluid, provided the sensitizing seminal fluid fractions are used as immunogens. Successful intravaginal graded challenge with unfractionated seminal fluid has been reported in a few cases, but the duration of protection is unknown. **C**
44. Localized and/or systemic seminal plasma hypersensitivity is not associated with infertility. **D**

Diagnosis

Anaphylaxis caused by coital exposure to human seminal fluid is a rare occurrence. Since the initial report in 1958, approximately 30 cases of seminal fluid–induced anaphylaxis have been described.[145-147] All reactions have occurred in female patients during or after sexual intercourse. The vast majority of such reactions are caused

by IgE-mediated sensitization to human seminal plasma proteins with molecular weights ranging from 12 to 75 kd.[148-150] In rare cases spermatozoa have been identified as the source of allergens inducing a cell-mediated reaction.[151] Coital anaphylaxis has also been attributed to exposure to exogenous allergens transferred through semen during sexual intercourse. Such unusual reactions occur when a male partner ingests a food (eg, walnuts) or drug (eg, penicillin) to which there is established sensitization in the female partner.[152,153] Human anaphylaxis has also been described after repetitive coital exposure to canine seminal plasma.[154]

Seminal plasma hypersensitivity is essentially a diagnosis by exclusion. A detailed history is essential to rule out underlying causes, such as sexually transmitted diseases, latex sensitivity, or transfer of food or drug proteins from the male sexual partner to the female who might be sensitized to these agents or other contactants, such as fragrant sanitary napkins. Seminal plasma protein anaphylaxis begins within seconds to minutes after ejaculation and presents with a range of symptoms, including the following: 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.[155] Failure of condoms to prevent anaphylaxis suggests either incorrect condom technique or concurrent sensitization to latex.[156] Localized vulvar and vaginal burning might occur as isolated symptoms or in conjunction with itching and swelling after ejaculation. There is no evidence to support the contention that localized vaginal seminal plasma hypersensitivity increases susceptibility of the individual to have future systemic anaphylactic symptoms.

The most significant risk for seminal plasma protein anaphylaxis is in patients with a history of allergic asthma or atopic dermatitis.[146,150,157,158] However, anecdotal case reports of seminal fluid–induced anaphylaxis have occurred postpartum, after gynecologic surgery, and after injection of anti-Rh immune globulin.[146] It has not been established whether 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.[159] Anaphylactic events have been reported in women with multiple previous sexual encounters or in others after the first coital act.[146] Postcoital allergic reactions are not specific to one partner and almost always recur with different male partners. Surveys have indicated that most subjects with seminal plasma hypersensitivity are not generally promiscuous in that they typically have reported a history of less than 2 sexual partners.[146]

The diagnosis must be confirmed by means of demonstration of sensitization to seminal fluid proteins through *in vivo* and/or *in vitro* immunologic methods. Demonstration of increased serum specific IgE assays with both positive and negative control sera confirms sensitization.[149] On the basis of available data, *in vitro* tests (eg, RAST and ELISA) of serum specific IgE appear to be less sensitive than skin testing and could be due to the lack of reliable test allergens.[146] Thus a negative serologic test result for seminal plasma specific IgE does not exclude sensitization.

Because sensitive specific IgE assays are not readily available, skin prick testing with whole human seminal plasma from the male partner is recommended for initial screening of suspect cases. Before skin testing, the male donor must be screened for viral hepatitis, syphilis, and HIV infection, and if there is evidence of infection, *in vivo* procedures should not be performed. Whole seminal plasma is prepared from a fresh specimen of ejaculate. Semen is allowed to liquefy at room temperature and centrifuged at 4°C to separate seminal plasma containing supernatant from spermatozoa, which is then filter sterilized.[149-151] The male donor is also tested to control for irritant responses. A positive response is defined as a wheal of 3 mm greater than or equal to that produced with saline with a flare and a concomitant negative response in the male donor. Typically, intracutaneous skin testing to whole seminal plasma has not been performed as a screening test in that it has been previously demonstrated to result in a nonspecific irritant response. Therefore screening for seminal plasma hypersensitivity should be limited to skin prick testing to whole seminal fluid. It should be emphasized that protein allergens contained in whole seminal plasma might not be present in sufficient concentrations to elicit a positive response. Thus a negative skin prick test response to whole seminal plasma does not exclude allergic sensitization. In this case skin test reagents with high diagnostic sensitivity should be obtained by means of gel filtration (Sephadex G-100) of whole seminal plasma to isolate allergen-rich fractions.[149-151]

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.[160]

Treatment

Consideration must be given to the psychological effect of this condition on the patient, her spouse, and the future of their marital relationship. Couples should be informed that successful pregnancies have been achieved after artificial insemination with sperm washed free of seminal plasma.[159] Once the diagnosis is suspected, the patient must be advised to avoid coital exposure to seminal fluid. This can be achieved by means of either temporary cessation of intercourse or with the correct use of latex condoms. Coitus interruptus is often not successful because of 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 before engaging in sexual intercourse.[151,152] It is essential that patients and spouses be trained in the emergency use of subcutaneous epinephrine. Although there are reports of successful use of precoital treatment with antihistamines or intravaginal cromolyn sodium, these options have generally been ineffective in the prevention of severe anaphylaxis.[160]

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. Several (usually 4-7) fraction pools that correspond to different absorption peaks are collected by means of elution of whole seminal plasma over a Sephadex G-100 column.[148-151,161] Fraction pools are concentrated, quantitated for protein, and filter sterilized. *In vivo* allergenicity is evaluated by means of end point intracutaneous threshold testing. Because of its known immunosuppressive properties, the first fraction pool representing the initial absorption peak and containing high-molecular-weight proteins should not be used.[151] After obtaining informed consent, subcutaneous injections of allergenic fractions are administered by using a rapid immunotherapy program beginning with a concentration that is at least 2 log dilutions higher than the end point threshold concentration. Because systemic reactions can occur during immunotherapy, emergency equipment necessary for treating anaphylaxis must be available. Injections are continued every 15 to 20 minutes until the highest available protein concentration is achieved for each allergenic fraction. Decreased or absent skin reactivity to treatment fractions and disappearance of serum specific IgE observed after immunotherapy has indicated that desensitization can be accomplished at the conclusion of the immunotherapy protocol. In highly sensitive patients injections might only be advanced over a period of weeks to months. An intravaginal instillation of fresh ejaculate should be used to confirm the efficacy of treatment. If a challenge is well tolerated, unprotected coitus can then be safely initiated. Intercourse must be continued on a regular schedule (2-3 times per week). Prolonged abstinence has resulted in loss of tolerance and recurrence of anaphylactic episodes.[149,151,155,161] If abstinence periods can be predicted, subcutaneous injections of relevant allergens might be resumed to prevent loss of tolerance.

Successful intravaginal graded challenges have been reported in women given diagnoses of human seminal plasma–induced anaphylaxis confirmed by means of skin prick test reactivity to whole seminal plasma.[162-167] Increasing 10-fold concentrations (1;10,000 to neat) of whole seminal plasma are deposited intravaginally at 20-minute intervals and followed by a frequent schedule of unprotected sexual intercourse. No procedure-related systemic reactions have been reported to date. This approach has been successful in preventing subsequent anaphylactic episodes. As with parenteral desensitization protocols, frequent intercourse (2-3 times per week) is required to maintain the desensitized state. One case reported that abstinence for as short as 5 days resulted in recurrence of a postcoital reaction. The efficacy of intravaginal graded challenge is based entirely on single anecdotal reports. Because decreased percutaneous reactivity to seminal plasma has not been demonstrated, it is unknown whether the intravaginal approach represents true desensitization. Moreover, the duration of the protective effect is unknown. Graded intravaginal challenges have been less effective in women with localized seminal plasma–induced hypersensitivity reactions.[168]

Finally, it is very important to inform women with this problem that although seminal plasma hypersensitivity can cause significant stress on interpersonal relationships, it has no effect on their ability to get pregnant because it has not been associated with infertility.[166,168]

EXERCISE-INDUCED ANAPHYLAXIS

Summary Statements

45. Exercise-induced anaphylaxis is a form of physical allergy. Premonitory symptoms can include diffuse warmth, itching, and erythema. Urticaria generally ensues, with progression to confluence and often angioedema. Episodes can progress to include gastrointestinal symptoms, laryngeal edema, and/or vascular collapse. **B**
46. Factors that have been associated with exercise-induced anaphylaxis include medications (eg, aspirin or other nonsteroidal anti-inflammatory drugs) or food ingestion before and after exercise. **C**
47. Patients with exercise-induced anaphylaxis might have a higher incidence of personal and/or family history of atopy. **C**
48. Medications used prophylactically are not useful in preventing exercise-induced anaphylaxis. **C**
49. If exercise-induced anaphylactic episodes have been associated with the ingestion of food, exercise should be avoided in the immediate postprandial period. **C**
50. Patients with exercise-induced anaphylaxis should carry epinephrine and should wear and/or carry Medic Alert identification denoting their condition. They should have a companion with them when exercising. This companion should be versed in the use of an EpiPen. **D**

Exercise-induced anaphylaxis is a form of physical allergy. Initial symptoms typically include diffuse warmth, pruritus, erythema, and urticaria, with progression to angioedema, gastrointestinal symptoms, fatigue, laryngeal edema, and/or vascular collapse.[169] Symptoms can persist for 30 minutes to hours. Transient loss of consciousness occurs in about a third of patients because of vascular collapse, whereas symptoms of upper respiratory tract obstruction occur in almost two thirds of patients.

Jogging is a common activity precipitating attacks, but brisk walking, bicycling, racquet sports, skiing, and aerobic exercise might also be associated with such anaphylactic reactions.[170-172] In some patients exercise-induced anaphylaxis will only occur after ingestion of a specific food or medication, such as aspirin or other nonsteroidal anti-inflammatory agents. Ingestion of these medications before exercise has been reported by 13% of affected individuals,[173] and their elimination might enable the patient to tolerate exercise. Exercise-induced anaphylaxis in the postprandial state, without identification of a specific food, occurred in 54% of the respondents in the same survey. Exercise-induced anaphylaxis has also been reported when a certain food is ingested after, as well as before, exercise (see food allergy parameter). In some patients specific foods have been shown to trigger these reactions. Elimination of these foods might allow the patient to exercise without anaphylaxis development.[113,173-176] These patients might ingest these foods without anaphylaxis development if they do not exercise for 4 to 6 hours after eating them. Provocation of exercise-induced anaphylaxis with a latency period after food consumption of 24 hours has been reported.[113] For this reason, it is prudent to individualize this management recommendation, particularly for individuals with postparandial (nonfood specific) exercise-induced anaphylaxis. It should also be clear that these foods might be ingested in the absence of exercise without difficulty. Thus both exercise and food ingestion are necessary to produce the reaction. Individuals who have exercise-induced anaphylaxis might have a higher incidence of a personal and/or family history of atopy.[170]

Exercise-induced anaphylaxis should be distinguished from other exercise-associated medical conditions. Arrhythmias or other isolated cardiovascular events related to exercise can be first seen with vascular collapse but are not associated with pruritus, erythema, urticaria-angioedema, or upper respiratory obstruction. Patients who have exercise-induced anaphylaxis usually have wheezing in association with other symptoms of anaphylaxis, whereas patients who have exercise-induced bronchospasm have symptoms referable only to the lower respiratory tract.

Cholinergic urticaria is a physical allergy characterized by the development of punctate (1-3 mm diameter), intensely pruritic wheals with erythematous flaring after an increase in core body temperature or stress. A minority of individuals with exercise-induced anaphylaxis have cutaneous lesions consistent with cholinergic urticaria. Classic cholinergic urticaria elicited by means of exercise, as noted above, is characteristically associated with an increase in the core body temperature without vascular collapse. However, in 2 of 16 patients who did not have punctate urticaria with increase of core body temperature, a syndrome resembling exercise-induced anaphylaxis was seen with punctate urticaria progressing to collapse.[171] Unlike cholinergic urticaria, simply increasing the core body temperature does not necessarily produce symptoms of exercise-induced anaphy-laxis. In addition, these syndromes might rarely appear concurrently.

A detailed history of symptoms associated with the first episode, as well as previous attacks, should be obtained. The history should include details concerning activities and ingestants that might precipitate an episode of anaphylaxis. Particular attention should be given to the antecedent use of aspirin or other nonsteroidal anti-inflammatory agents, as well as any seasonality to the attacks.

Prophylactic use of H_1 and H_2 antihistamines has generally not been effective in preventing exercise-induced anaphylaxis.[172] This is not without controversy, however, because reports have demonstrated in selected patients that antihistamine prophylaxis might help reduce the frequency and/or intensity of attacks.[177,178]

Early recognition of the prodromal manifestations of exercise-induced anaphylaxis is extremely important, with discontinuation of exercise at the earliest symptom. Modification of the exercise program by means of reduction in intensity or duration might be helpful in reducing episodes of exercise-induced anaphylaxis. Avoidance of exercise for 4 to 6 hours after eating is important in those individuals with documented exercise-induced anaphylaxis after food ingestion.

The emergency management of exercise-induced anaphylaxis is the same as that of anaphylaxis of other causes. The early administration of epinephrine is essential. Intravenous volume replacement, adequate oxygenation, and vigilance for upper airway compromise, with possible endotracheal intubation or tracheostomy, might also be required. H_1 blocking agents might be helpful but should not be relied on to abort the attack.

Affected individuals should discontinue exercise at the earliest symptom consistent with exercise-induced anaphylaxis, usually pruritus and cutaneous warmth or erythema (flushing). Such individuals should be accompanied during exercise by a companion aware of their condition and capable of providing emergency assistance. Patients with exercise-induced anaphylaxis should have injectable epinephrine available at all times of exercise for self-administration in the event of symptoms. Any patient who has a history consistent with food-dependent exercise-induced anaphylaxis should be told not to exercise for 4 to 6 hours after eating. There is controversy as to whether all patients should similarly be told not to exercise postprandially, and the decision to do so in such instances remains a clinical decision for the physician.

IDIOPATHIC ANAPHYLAXIS

Summary Statements

51. The symptoms of idiopathic anaphylaxis are identical to those of episodes related to known causes. **C**
52. Patients with idiopathic anaphylaxis should receive an intensive evaluation, including a meticulous history to rule out a definite cause of the events. **C**

53. There might be a need for specific laboratory studies to exclude systemic disorders, such as systemic mastocytosis. This might include a serum tryptase measurement when the patient is asymptomatic, measurement of the ratio of β-tryptase to total tryptase during an event, and selective allergy skin testing. **C**

In spite of efforts to define the pathogenesis of idiopathic anaphylaxis, we still do not know why patients experience these attacks. However, it is known that some might exhibit activated T cells shortly after episodes.[179]

The diagnosis of idiopathic anaphylaxis must be considered in those cases of anaphylaxis for which neither a causative allergen nor an inciting physical factor can be identified. Episodes can occur in both adults and children.[180-184]

The presenting manifestations of idiopathic anaphylaxis are identical to those of any form of anaphylaxis.[2] The vast majority of cases occur in adults, but there have been reports of episodes in children as well. Fatalities are rare but have occurred.[185]

The diagnosis of idiopathic anaphylaxis is a diagnosis of exclusion. Patients with idiopathic anaphylaxis should receive intensive evaluation, including a careful history with analysis of the events surrounding the development of the episodes. Clinical evaluation might indicate the need for specific laboratory studies, which might help to exclude an underlying systemic disorder, such as systemic mastocytosis. In addition, selective skin testing to foods (and if indicated to fresh food extracts) might be helpful.[103]

Because systemic mastocytosis can present as anaphylaxis of unknown cause, it is important to rule out this condition. The definitive test in this condition is a bone marrow biopsy, but serum tryptase levels can be helpful. In systemic mastocytosis, the baseline level (level obtained during an asymptomatic period) of total tryptase can be increased, whereas this is not the case in idiopathic anaphylaxis. In addition, the total β-tryptase to total tryptase ratio in systemic mastocytosis is usually greater than 20, whereas it is 10 or less in idiopathic anaphylaxis.[186]

The treatment of the acute episode is the same as the treatment for any other form of anaphylaxis. Various protocols have been published to prevent recurrent episodes. These protocols have recommended the administration of H_1 and H_2 antagonists, β-agonists, antileukotrienes, and corticosteroids. All of these have proved successful in individual cases. The decision to institute preventive therapy is under the aegis of the treating physician, and the decision to use a preventive protocol and the medications used should be based on the frequency and severity of recurrent episodes. Patients should of course be supplied a kit for the self-injection of epinephrine and should be instructed in its use. They should also have Medic Alert identification because syncope can occur during these events. Fortunately, the symptoms of most patients improve with time, and many undergo complete remission.[59,187,188]

ANAPHYLAXIS AND ALLERGEN IMMUNOTHERAPY VACCINES
Summary Statements

54. There is a small risk of near-fatal and fatal anaphylactic reactions to allergen immunotherapy injections. **C**

The rate of fatal anaphylaxis to allergen immunotherapy injections is approximately 1 in 2.5 million injections.[66,189-191] The rate of systemic reactions to allergen immunotherapy injections is approximately 0.5%.[192] Thus although severe systemic reactions to allergen immunotherapy are uncommon, physicians and patients should be prepared for possible systemic reactions after immunotherapy.

55. Patients with asthma, particularly poorly controlled asthma, are at higher risk for serious systemic reactions to allergen immunotherapy injections **(C)**. Patients taking β adrenergic blocking agents are at higher risk for serious systemic reactions to allergen immunotherapy injections **(B)**.

Numerous studies suggest that patients with asthma, particularly poorly controlled asthma, are at higher risk for serious systemic reactions to allergen immunotherapy injections.[66,189,190,192-195] However, allergic asthma is an important clinical indication for allergen immunotherapy. Caution is advised when administering allergen immunotherapy vaccine if asthma is severe or poorly controlled. Many practitioners measure the peak expiratory flow rate before administering the allergen vaccine.

Patients receiving β-adrenergic blocking agents are at increased risk for more serious anaphylaxis.[66,196] Thus β-adrenergic blockade is a relative contraindication for allergen immunotherapy. The benefits of allergen immunotherapy might outweigh the risk of anaphylaxis to the allergen vaccine for patients with hypersensitivity to stinging insects.

56. 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**

Allergen immunotherapy vaccines should be administered only by health care professionals trained in the recognition and treatment of anaphylaxis. Allergen immunotherapy should be administered only in health care facilities with the proper equipment for the treatment of anaphylaxis. Such equipment includes epinephrine, oxygen, antihistamines, corticosteroids, vasopressors, oral airway, and equipment for the administration of intravenous fluids and medications.

Allergen immunotherapy should be administered in clinics with policies and procedures that minimize the risk of anaphylaxis. These policies and procedures should reduce the risk of error, ensure proper

training of personnel, and facilitate treatment of anaphylaxis (practice parameters).

Most systemic reactions occur within 20 or 30 minutes after allergen vaccine administration, although late reactions do occur.[193,197] To better recognize and treat anaphylactic reactions, patients should wait in clinic for 20 or 30 minutes after receiving an allergen immunotherapy injection. In addition, patients who are at increased risk of systemic reactions, particularly if they previously have had a systemic reaction more than 30 minutes after an injection, might need to carry injectable epinephrine.[198] These patients should be instructed in the use of epinephrine to treat a systemic reaction that occurs after they have left the physician's office or other location where the injection was given. Such patients might also need to remain in the physician's office more than 30 minutes after an injection.

ANAPHYLAXIS TO DRUGS
Summary Statements

57. In most cases low-molecular-weight medications induce an IgE-mediated reaction only after combining with a carrier protein to produce a complete multivalent antigen. **B** A few drugs might elicit IgE-mediated reactions without first combining with a carrier protein.
58. Penicillin is the most common cause of drug-induced anaphylaxis. **C**
59. Penicillin spontaneously degrades to major and minor antigenic determinants, and skin testing with reagents on the basis of these determinants yields negative results in about 90% of patients with a history of penicillin allergy. **B**
60. The negative predictive value of penicillin skin testing (for immediate-type reactions) is between 97% and 99% (depending on the reagents used), and the positive predictive value is at least 50%. **B**
61. The extent of allergic cross-reactivity between penicillin and cephalosporins is unknown but appears to be low. A small percentage of patients proved to have penicillin allergy through penicillin skin testing react to cephalosporin challenges. **C**
62. Patients with a history of penicillin allergy who have negative penicillin skin test responses might safely receive cephalosporins. **B**
63. Patients with a history of penicillin allergy who have positive penicillin skin test responses might (1) receive an alternate (non–β-lactam) antibiotic, (2) receive a cephalosporin through graded challenge, or (3) receive a cephalosporin through rapid desensitization. **F**
64. Aztreonam does not cross-react with other β-lactams except ceftazidime, with which it shares a common R-group side chain. **B**
65. Carbapenems should be considered cross-reactive with penicillin. **C**
66. 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**
67. Aspirin and nonsteroidal anti-inflammatory drugs are the second most common cause of drug-induced anaphylactic reactions. **C**
68. Anaphylactic reactions to aspirin and nonsteroidal anti-inflammatory drugs appear to be medication specific and do not cross-react with structurally unrelated aspirin or other nonsteroidal anti-inflammatory drugs. **D**
69. Anaphylactic reactions to aspirin and nonsteroidal anti-inflammatory drugs appear to be medication specific and do not cross-react with structurally unrelated aspirin or other nonsteroidal anti-inflammatory drugs. **D**

Introduction

Medications are a common cause of anaphylaxis. Drug-induced anaphylactic reactions are due to the development of drug-specific IgE antibodies during a preceding period of sensitization, typically during a previous course with the same or cross-reacting compound. The relatively low molecular weight of most drugs prevents them acting as complete antigens and inducing an immune response. In most cases medications must first combine with larger carrier molecules (eg, normal tissue or serum proteins) to form an immunogenic multivalent antigen. A few drugs might elicit IgE-mediated reactions without first combining with a carrier protein. Furthermore, most drugs are not chemically reactive in their native state. They need to undergo degradation or metabolism to produce reactive intermediates, which then covalently bind to host proteins and might lead to an allergenic response with the production of IgE antibodies. In some cases the allergenic determinants against which specific IgE is directed are known, such as with penicillin, and immediate type skin testing can be performed to aid in diagnosis. In most situations the allergenic determinants are unknown, and the diagnosis can only be made clinically.

Some drugs are also capable of causing anaphylactoid reactions, which are due to direct nonimmunologic mast cell degranulation and do not require a preceding sensitizing period. Anaphylactoid reactions typically occur on initial exposure to a given drug and do not require a period of sensitization. Some medications are capable of causing both anaphylactic and anaphylactoid reactions, and because of this, it might be difficult to determine the cause of a given reaction.

Antibiotics

Penicillins. Penicillin is the most common cause of drug-induced anaphylaxis.[199] Under physiologic conditions, penicillin spontaneously degrades to reactive intermediates, which are broadly categorized into major and minor antigenic determinants. Because the immunochem-

istry of penicillin is well characterized, validated skin testing reagents representing the various allergenic determinants have been developed. In large-scale studies about 90% of patients with a history of penicillin allergy have negative penicillin skin test responses.[200,201]

The positive predictive value of penicillin skin testing is 50% or greater.[201,202] Patients with positive penicillin skin test responses should receive an alternate antibiotic or undergo rapid desensitization if administration of penicillin is mandated. The negative predictive value of penicillin skin testing (for immediate-type reactions) is between 97% and 99%, depending on the skin test reagents used.[200,201,203] Patients with negative penicillin skin test responses might be safely treated with penicillin, and depending on the reagents used for skin testing, the therapeutic dose might be preceded by a test dose.

Penicillin skin testing is safe in that the risk of inducing serious reactions during properly performed penicillin skin testing is comparable with the risk of other types of skin testing.[204] Penicillin skin testing itself might sensitize a very small proportion of patients.[205] Skin testing with semisynthetic penicillins, such as ampicillin or amoxicillin, is not standardized, and its predictive value is unknown. Penicillin skin testing should not be performed on patients with histories of severe non–IgE-mediated allergic reactions to penicillin, such as Stevens-Johnson syndrome or toxic epidermal necrolysis.

Cephalosporins. Penicillins and cephalosporins share a common β-lactam ring, but the extent of allergic cross-reactivity between the 2 families appears to be relatively low. Recent studies demonstrated no serious allergic reactions in large groups of patients with a history of penicillin allergy who were treated with cephalosporins.[206,207] Patients in these retrospective studies, however, were given diagnoses of penicillin allergy on the basis of self-report. Patient history is known to be poor predictor of true penicillin allergy in that about 90% of patients with such a history turn out to have negative penicillin skin test responses and are able to tolerate penicillin.[200,201] A review of the published literature showed that among patients with a history of penicillin allergy who were proved to have positive penicillin skin test responses, only a small percentage of patients experienced an allergic reaction on being challenged with cephalosporins.[208] However, fatalities have occurred when patients are not skin tested for penicillin and given cephalosporins.[209] There are distant case reports of cephalosporin-induced anaphylactic reactions in patients with a history of penicillin allergy,[210,211] but these patients did not undergo penicillin skin testing, and early cephalosporins were also known to contain trace amounts of penicillin.

Patients with a history of penicillin allergy who have negative penicillin skin test responses might receive cephalosporins because they are at no higher risk of experiencing allergic reactions.[212] In patients with a history of penicillin allergy who have positive penicillin skin test responses, the physician has 3 options: (1) administration of an alternate non–β-lactam antibiotic; (2) administration of a cephalosporin through graded challenge; or (3) desensitization to the cephalosporin.[212]

Other β-lactam antibiotics. Monobactams (aztreonam) do not-cross react with penicillin or other β-lactams, aside from ceftazadime, with which it shares an identical R-group side chain.[213] Therefore patients allergic to penicillin and other β-lactams (except for ceftazidime) might safely receive aztreonam. Similarly, patients allergic to aztreonam might safely receive other β-lactams, except for ceftazidime.

Skin test studies indicate allergic cross-reactivity between carbapenems and penicillin.[214] Although clinical challenge studies in patients with penicillin allergy are lacking, carbapenems should be considered cross-reactive with penicillin.

Non–β-lactam antibiotics. 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 lack of knowledge (in most cases) of the relevant metabolites and allergenic determinants. Skin testing with the native antibiotic can yield some useful information because if a nonirritating concentration is used, a positive result suggests the presence of drug-specific IgE antibodies.[215] However, the positive predictive value of such testing is unknown, and the negative predictive value is even less certain. Therefore diagnosis of anaphylactic reactions to non–β-lactam antibiotics is primarily based on the patient's history.

Aspirin and nonsteroidal anti-inflammatory drugs. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), including COX-2–specific inhibitors, have all been described to cause anaphylactic reactions. Aspirin and NSAIDs appear to be the second most common cause of drug-induced anaphylaxis (after penicillin).[2,216] Anaphylactic reactions are unrelated to other reactions caused by these drugs, such as respiratory reactions and exacerbations of chronic idiopathic urticaria.[217] Although the reactions are referred to as anaphylactic, in most cases efforts to detect drug-specific IgE antibodies (through skin testing or *in vitro* testing) have been unsuccessful. The reactions are assumed to be anaphylactic because generally patients are able to tolerate the drug for a period of time before a reaction ensues. Anaphylactic reactions to aspirin and NSAIDs appear to be medication specific in that allergic patients are able to tolerate other NSAIDs, but this is largely based on clinical experience rather than large-scale challenge studies.[217]

Cancer chemotherapeutic agents. Anaphylaxis to anticancer chemotherapy drugs is being encountered more frequently because use of these drugs has increased,[218] particularly the platinum-containing drugs, such as cisplatinum and carboplatinum. In some instances the solvent in which these drugs are formulated (Cremophor-L) might cause an anaphylactoid reaction.[219] Such anaphylactoid reactions to the drug product must be distinguished from anaphylaxis because of the drug. Skin testing to these agents is helpful in determining whether sensitivity exists and at what dose to proceed with sensitization if this is necessary.[220]

PREVENTION OF ANAPHYLAXIS

Summary Statements

70. Major risk factors related to anaphylaxis include, but are not limited to, prior history of such reactions, β-adrenergic blocker exposure, or atopic background. Atopic background might be a risk factor for venom- and latex-induced anaphylaxis and possibly anaphylactoid reactions to radiographic contrast material but not for anaphylactic reactions to medications.

71. Avoidance measures are successful if future exposure to drugs, foods, additives, or occupational allergens can be prevented. Avoidance of stinging and biting insects is also possible in many cases. Prevention of systemic reactions during allergen immunotherapy are dependent on the specific circumstances involved.

72. 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.

73. Pharmacologic prophylaxis should be used to prevent recurrent anaphylactoid reactions to radiographic contrast material, fluorescein, as well as to prevent idiopathic anaphylaxis. Prophylaxis with glucocorticosteroids and antihistamines markedly reduces the occurrence of subsequent reactions.

74. Allergen immunotherapy with the appropriate stinging insect venom should be recommended for patients with systemic sensitivity to stinging insects because this treatment is highly (90% to 98%) effective.

75. Desensitization to medications that are known to have caused anaphylaxis can be effective. In most cases the effect of desensitization is temporary, and if the medication is required some time in the future, the desensitization process must be repeated.

76. Patient education might be the most important preventive strategy. Patients should be carefully instructed about hidden allergens, cross-reactions to various allergens, 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.

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%, and life-threatening reactions occur with a frequency of less than 0.1% with conventional high-osmolality RCM.[221] Among the 5% to 8% of patients who experience an adverse reaction to conventional RCM, most have minor reactions that require no specific treatment.[222] Moderate reactions, such as severe vomiting, diffuse urticaria, or angioedema, that require therapy occur in about 1% of patients who receive RCM.

Although studies quote a wide spectrum of mortality, a reasonable estimate is one in every 75,000 patients who receive RCM.[223] With the recent development of lower-osmolality RCM, it appears that the overall risk of anaphylactoid reactions is decreased to about one fifth that of conventional RCM.[224]

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 can range from as low as 16% to as high as 44%.[225,226] Other patients at increased risk are asthmatic and atopic patients, as well as those receiving β-adrenergic blocking agents and patients with cardiovascular disease.[227-229] Anaphylactoid reactions have occurred when RCM is used for hysterosalpingograms, myelograms, and retrograde pyelograms.[225] With pretreatment and the use of lower-osmolarity agents, the risk can be reduced to approximately 1%.[230]

Anaphylactoid reactions to RCM are independent of the dosage or concentration of RCM. Clinically, these reactions are identical to immediate hypersensitivity IgE-mediated reactions (anaphylaxis) but do not appear to involve IgE or any other immunologic mechanism.[228]

In almost all instances, the infusion of RCM should be discontinued if symptoms begin. The treatment of anaphylactoid reactions to RCM is not different than the treatment of anaphylactic-anaphylactoid reactions in other settings.

If the patient has a history of a prior anaphylactoid reaction to RCM, pretreatment regimens for prevention of repeat anaphylactoid reactions have consisted of oral glucocorticosteroids, H_1 and H_2 antihistamines, and other medications, such as ephedrine. 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. However, modifications to this regimen have included lower doses of glucocorticosteroids, oral rather than intramuscular diphenhydramine or other H_1 antihistamines, additional use of H_2 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.[229]

In a setting in which RCM is being administered, a differential diagnosis might include adult respiratory distress syndrome or noncardiogenic pulmonary edema. In at least 2 reports of failure of standard pretreatment regimens to prevent anaphylactoid reactions, the initial reactions were apparently caused by noncardiogenic

pulmonary edema rather than anaphylactoid reactions.[231,232] In addition, RCM can cause intravascular volume expansion and precipitate cardiogenic pulmonary edema in patients with ischemic cardiac disease.

Anaphylactoid reactions in patients receiving β-adrenergic blocking agents might require more intensive and prolonged treatment. Therefore a careful benefit-risk assessment should be made in patients receiving β-adrenergic blocking agents if there is a pre-existing increased risk of having an anaphylactoid reaction to RCM. There is no evidence that the inorganic iodine levels present in seafood are related to adverse events from RCM.

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