CORRECTION

"The Diagnosis and Management
of Anaphylaxis"

CORRECTION

The following correction applies to the practice parameter by Nicklas et al entitled "The Diagnosis and Management of Anaphylaxis," which appeared in volume 101, part 2, pp S465-S528, 1998. of *The Journal.*

On p S470, the dosage information given in the second column for epinephrine is incorrect. The text should read "Intravenous epinephrine should be administered either by using a formulation of 1:10,000 (0.1 mg/ml) epinephrine or by first diluting a 1:1000 (1 mg/ml) dilution (wt/vol) of epinephrine to a 1:10,000 dilution. The infusion of either preparation should be initially titrated at 1 µg/min, which can be increased to 2 to 10 µg/min. These doses may be easier to administer by using a 1:100,000 (0.01 mg/ml) dilution."

Also, please note the following institutional affiliation: John F. Erffmeyer, MD, Ochsner Clinic of Baton Rouge, Baton Rouge, Louisiana. Dr. Erffmeyer was a member of the workgroup that initially developed the practice parameter entitled "The Diagnosis and Management of Anaphylaxis" and contributed significantly to the development of this parameter. His institutional affiliation was not available at the time the issue went to press.

THE DIAGNOSIS AND MANAGEMENT OF ANAPHYLAXIS

These parameters were developed by the
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THE DIAGNOSIS AND MANAGEMENT OF ANAPHYLAXIS

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* Parameters. 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 the ACAAI should be directed to the Executive Offices of the AAAAI, the ACAAI, and the Joint Council of Allergy, Asthma and Immunology.

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I. Preface

Prevention of anaphylaxis and anaphylactoid reactions should be of paramount concern to all physicians. It is imperative that all health care workers be familiar with the signs and symptoms of anaphylactic events and the need for rapid diagnosis and treatment. These reactions, more than any other type of life-threatening event, can be unexpected complications of medical care. The difference between survival and death may ultimately depend on the physician's immediate recognition and diagnosis, followed by rapid and appropriate therapy.

Most of these reactions occur very rapidly, are often unanticipated, and may have dramatic effects. Even when there are mild initial symptoms, the potential for progression to a severe and even irreversible outcome must be appreciated. Any delay in recognizing the initial signs and symptoms of anaphylaxis can result in death caused by airway obstruction or vascular collapse.

There are a multitude of potential exposures in the patient's environment that can be implicated as precipitants of an anaphylactic or anaphylactoid event. Frequently, a complex clinical presentation requires the involvement of the allergy-immunology specialist, who possesses particular training and skills to evaluate and appropriately treat these high-risk individuals.

The approaches to the diagnosis and management of anaphylaxis represent general agreement of a panel of clinicians experienced in caring for patients with a history of anaphylactic or anaphylactoid reactions and has been reviewed and agreed upon by a large number of individuals in the specialty of allergy-immunology. It is recognized that there are different, although appropriate, ways of approaching the diagnosis and management of anaphylaxis. In addition, particular features in individual patients necessitate a degree of flexibility in therapeutic strategies.

Where indicated, what was considered useful background information has been discussed, but an attempt was made to keep this document succinct and relevant to the diagnosis and treatment of anaphylaxis and anaphylactoid reactions. With this goal in mind, only agents that are general prototypes of anaphylaxis or anaphylactoid reactions are included. Thus a number of specific drugs, such as antibiotics, as well as biologic modalities, are not discussed. Each section of the document is organized into a text with preceding summary statements. These summary statements reflect the editors' consensus on the key aspects of each section. In addition, algorithms for the evaluation and treatment of anaphylaxis and anaphylactoid reactions, with appropriate annotations, are provided to facilitate clinical decisions.

The editors thank those within the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology who have supported and encouraged this project, in particular Sue Grupe, who was instrumental in the preparation of this document. We also thank those individuals who have donated their time and energy to preparing the sections that form the foundation for this very important document.

II. Algorithm for initial evaluation of a patient with a past history of anaphylaxis (Fig. 1)

ANNOTATIONS: INITIAL EVALUATION OF A PATIENT WITH A PAST HISTORY OF ANAPHYLAXIS

Annotation 1: Does the patient present with a history suggestive of previous anaphylaxis?

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

The history should concentrate on agents encountered before the reaction. Whenever appropriate, information should be obtained from not only the patient but also from family members or other witnesses. The complete sequence of events must be reviewed, with special attention paid to cardiorespiratory symptoms. Medical records, including medication records, can often be useful in evaluating the history, physical findings, and treatment of the clinical event. In addition, the results of any previous laboratory studies (e.g., serum tryptase), may be helpful in making the diagnosis of anaphylaxis or distinguishing it from other entities.

Annotation 1A: Consider consultation with allergist/immunologist

Patients with anaphylaxis may 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: Consider other diagnoses

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

Annotation 3: Does the history suggest a specific cause of anaphylaxis?

A detailed and complete allergy history may suggest a specific cause of anaphylaxis, such as insect stings or bites, foods, drugs (e.g., penicillin), allergenic extracts, biologics (e.g., insulin), vaccines (e.g., avian-based vaccines), diagnostic testing materials (e.g., radiocontrast material), latex, seminal fluid, or exercise. Patient diaries may 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 allergy skin tests, in vitro specific IgE tests, and/or challenge tests appropriate?

Allergy skin tests, in vitro specific IgE tests, and/or challenge tests may be appropriate to help define the cause of the anaphylactic episode. However, the history may 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 may be circumstances where allergy skin tests, in vitro specific IgE tests, and/or challenge tests may not be warranted. In general, this may apply when the clinician (with 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 may be so strong that testing is unnecessary (or dangerous). Conversely, the medical history of anaphylaxis may be sufficiently mild or weak that management can proceed in the absence of testing. If avoidance can be easily and safely accomplished, testing may not be necessary.

Furthermore, testing or challenge with reagents to a suspected allergen may not be available, or the accuracy of the test may be in question. In addition, for patients with a history of anaphylaxis, challenge tests (and to a lesser extent skin tests) may 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
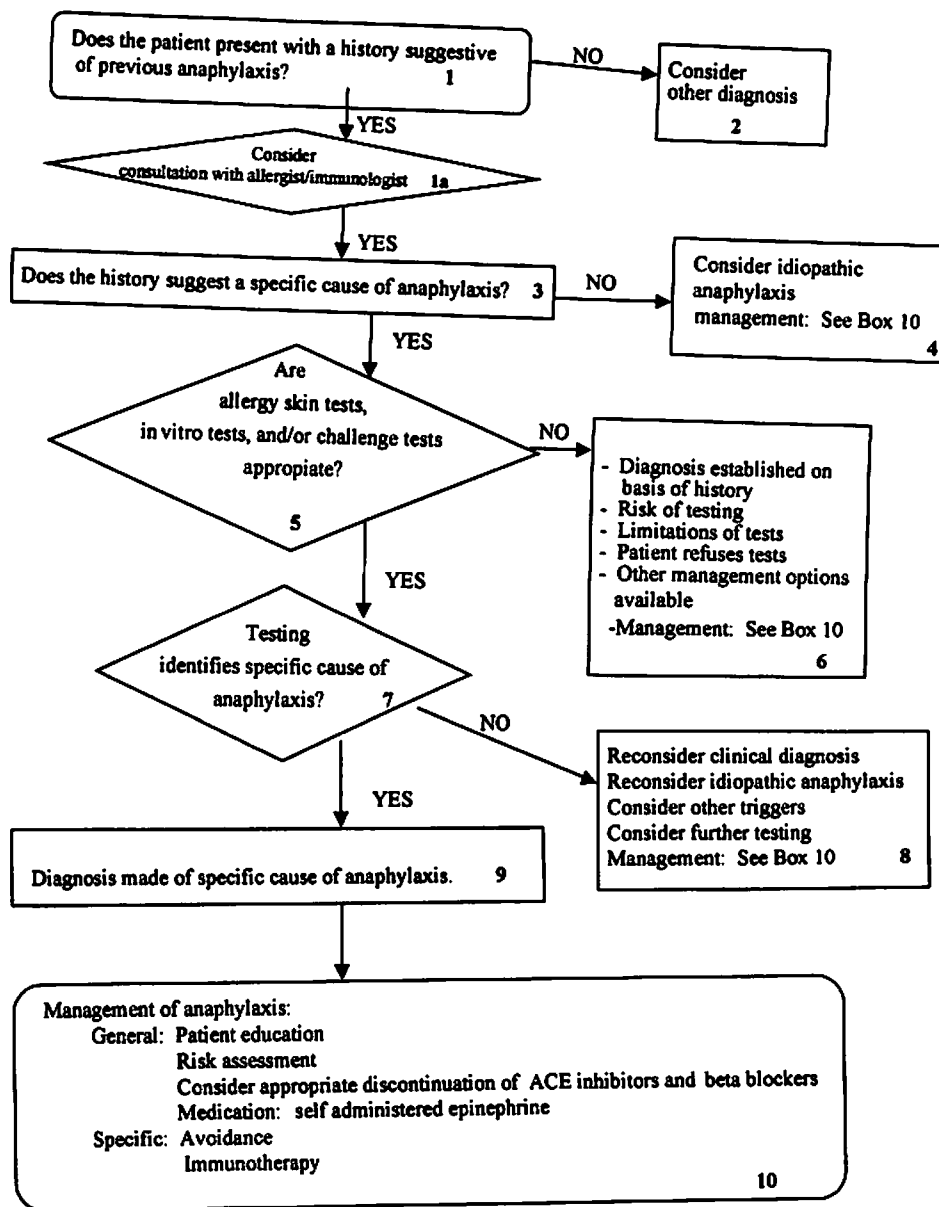
FIG. 1. Algorithm for initial evaluation of a patient with a past history of anaphylaxis.

this way include foods, medications, (e.g., penicillin and insulin), and stinging insects.

In general, skin testing is more sensitive than in vitro testing and is the diagnostic procedure of choice for evaluation of most potential causes of anaphylaxis (e.g., penicillin, insect stings, and foods). To obtain meaningful data regarding causative agents of anaphylaxis, it is essential that the correct technique for skin testing be used. When possible, standardized extracts should be used. If the skin testing extract has not been standardized (e.g., latex, protamine, or antibiotics other than penicillin), the clinical relevance of the results may be uncertain. If skin testing is performed, it should be done under the supervision of a physician who is experienced

in the procedure in a setting with appropriate rescue equipment and medication.

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

If tests for specific IgE antibodies (i.e., skin tests, in-vitro tests, or both) do not provide conclusive evidence of the cause of anaphylaxis, challenge with the suspected agent can be considered. Challenge procedures may also be appropriate in patients who develop non-IgE-mediated anaphylactic reactions (e.g., reactions

to Aspirin [ASA] or other nonsteroidal antiinflammatory drugs [NSAIDs]. 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

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 may be helpful include: serum tryptase, as well as urinary 5-hydroxyindolacetic acid, methylhistamine, and catecholamines. Idiopathic anaphylaxis is a diagnosis of exclusion (see section on 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 may be supported by the results of skin tests, in vitro IgE tests, and/or challenge tests (particularly double-blind, placebo-controlled challenge tests).

Annotation 10: Management of anaphylaxis

When anaphylaxis has occurred because of exposure to a specific agent (e.g., food, medication, or insect sting), patients should be educated about agents or exposures that would place them at risk for future reactions and be counselled on avoidance measures that may be used to reduce risk for such exposures. Patients who have had anaphylactic reactions to food should be instructed on how to read food ingredient labels to identify foods that they should avoid. Patients with anaphylaxis to medications should be informed about all cross-reacting medications that should be avoided. Should there be a future essential indication for use of incriminated medications, it may be helpful to educate patients about applicable management options (e.g., medication pretreatment and use of low osmolarity agents in patients with a history of reactions to radiographic contrast media or desensitization for drugs such as antibiotics). Patients who have had anaphylactic reactions to insect stings should be advised about avoidance measures to reduce the risk of insect stings and may be candidates for insect venom immunotherapy. Patients who have had anaphylaxis from exposures that may be encountered in nonmedical settings should carry self-injectable epinephrine for use if anaphylaxis develops. Many authorities would also advise such patients to carry adjunctive medications (e.g., antihistamines or corticosteroids) that may be used in addition to epinephrine. Patients should also carry identification cards or bracelets identifying them as prone to anaphylaxis and indicating the responsible agent. Patients taking angiotensin converting enzyme inhibitors or β-blockers may be at increased risk during anaphylaxis.

III. Algorithm for the treatment of acute anaphylaxis

ANNOTATIONS: TREATMENT OF ACUTE ANAPHYLAXIS (FIG. 2)

Annotation 1: Patient presents with possible/probable acute anaphylaxis

The onset and course of anaphylaxis can vary among patients. Of greatest concern are laryngeal edema and cardiovascular collapse, the most frequent causes of death. Urticaria and angioedema, although clearly the most common manifestations, may not occur at all in up to 10% to 15% of reactions.

Symptoms commonly occur within a few seconds or minutes after the patient is exposed to the causative agent. The more rapidly symptoms ensue, the more severe the reaction is likely to be. Sometimes the onset of symptoms can be delayed for several hours. Initially, the patient is often first seen with erythema or pruritus and progresses to urticaria and angioedema; with an accompanying sense of impending doom; complaints of dizziness or syncope with or without hypotension; and gastrointestinal symptoms that can include nausea, vomiting, cramping, and diarrhea.

Upper airway obstruction may be manifest by hoarseness, dysphonia, or difficulty swallowing. Lower airway involvement can appear as wheezing and chest tightness. In addition, nasal, ocular, and palatal pruritus are often observed. In some cases loss of consciousness or even a convulsive episode may be the initial sign of anaphylaxis.

Some patients have a late or second phase of anaphylaxis, even after complete resolution of the first response.

Annotation 2: Initial assessment, presentation indicates acute anaphylaxis?

The initial assessment should determine the nature and progression of the clinical event. The clinical event should be compatible with acute anaphylaxis (see section entitled "Evaluation and management of a patient with a history of anaphylaxis"). The history may reveal the cause of the reaction. Evaluation should include the upper and lower airways (evidence of edema, stridor, dyspnea, wheezing, or apnea), the cardiovascular system (hypotension or syncope), the skin (urticaria, angioedema, or flushing), the gastrointestinal system (vomiting and diarrhea), and the state of consciousness.

Annotation 3: Consider atypical presentation: consider other diagnosis

The differential diagnosis of acute anaphylaxis is very broad, and the presentation of acute anaphylaxis may be variable. Anaphylaxis can present as unexplained syncope, an acute cardiac event, or sudden death as well as urticaria, angioedema, dyspnea, wheezing, gastrointesti-nal distress or hypotension. A partial differential diagnosis list of acute anaphylaxis includes acute urticaria, angioedema, asthma, hyperventilation syndrome or panic attack, vasovagal reaction, ischemic heart disease, cardiac arrhythmia, seizure, carcinoid syndrome, and mastocytosis. (For a more complete list, see the annotation for Box 2 in Fig. 1).

Annotation 4: Evaluate clinical status (airway, cardiopulmonary, etc.). Is episode life threatening?

Anaphylaxis may be life threatening. Immediate evaluation of the patient is essential to determine (1) airway patency, (2) blood pressure, and (3) cardiac status. The patient may have life-threatening symptoms within minutes, or they may develop as the anaphylaxis episode progresses. Signs and symptoms of potentially life-threatening anaphylaxis include stridor, respiratory distress, wheezing, hypotension, cardiac arrhythmia, shock, seizures, and loss of consciousness. Such patients require immediate treatment.

Annotation 5: Consider epinephrine, antihistamines, and corticosteroids

Patients who do not appear to have life threatening symptoms on initial presentation may progress to life threatening anaphylaxis. Early administration of medications may be beneficial. Consider:

1. *Epinephrine.* The initial adult dose may range from 0.2 ml to 0.5 ml of a 1:1000 (wt/vol) dilution (0.2 to 0.5 mg base) subcutaneously or intramuscularly. This may be repeated every 10 to 15 minutes as needed up to a maximum of 1 mg per dose. The dose in children is 10 μg (0.01 mg) per kilogram body weight up to a maximum of 500 μg (0.5 mg) per dose or 0.5 ml of 1:1000 (wt/vol). This dose can be repeated every 15 minutes for two doses and then every 4 hours as needed. There is evidence that more rapid systemic absorption and higher peak plasma levels occur after intramuscular than after subcutaneous administration.
2. *Diphenhydramine.* 1 to 2 mg/kg or 25 to 50 mg/dose (parenterally).
3. Corticosteroids may also be administered. However, the efficacy of corticosteroids in acute anaphylaxis or in reducing a late anaphylactic reaction has not been clearly established.

Annotation 6: Emergency care

Life-threatening anaphylaxis requires immediate administration of epinephrine (as discussed in annotation 5) and may require other immediate measures for support of cardiorespiratory status. Cardiopulmonary
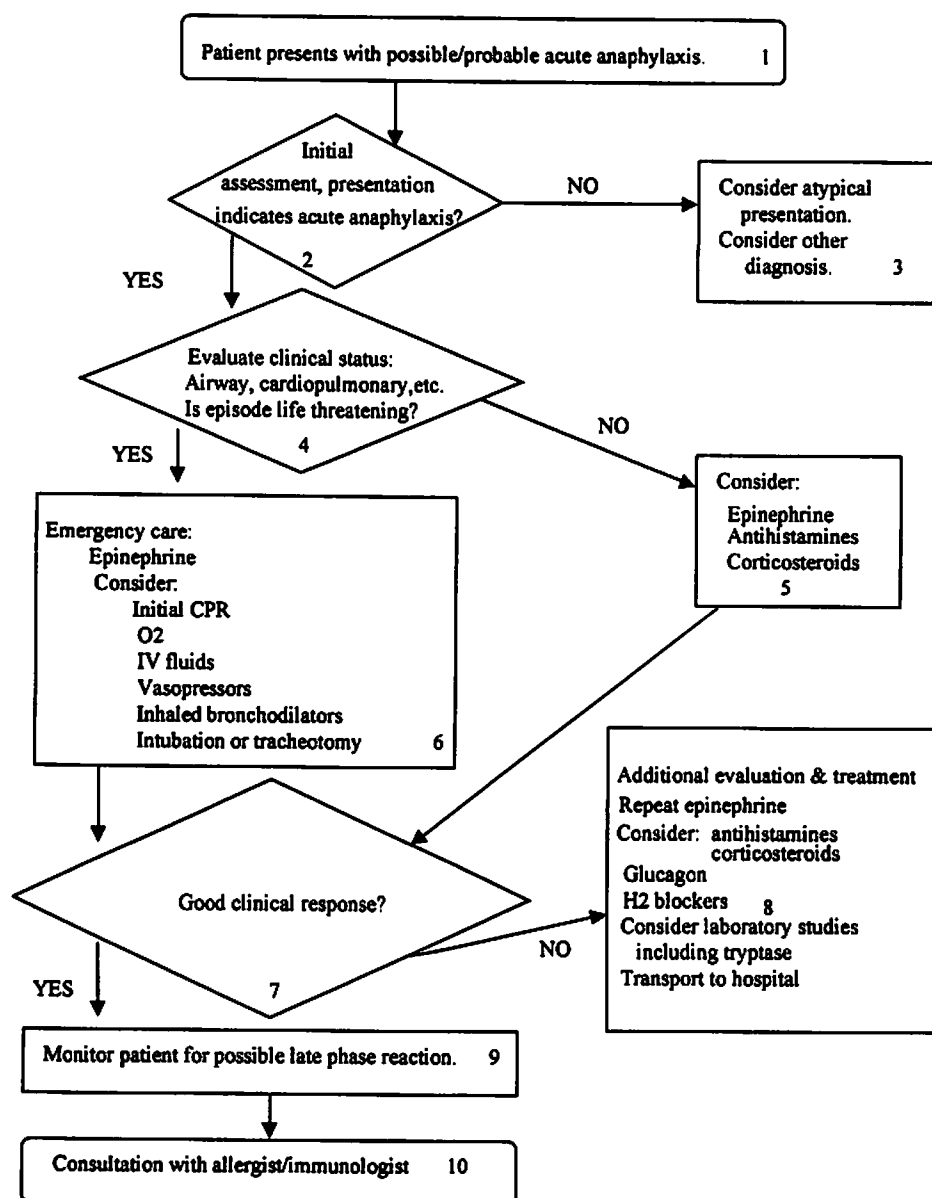
FIG. 2. Algorithm for the treatment of acute anaphylaxis.

resuscitation (CPR) should be instituted if there is loss of circulation or respiration. Maintenance of an airway with an oropharyngeal airway device or tracheotomy may be required. Oxygen should be administered if there is circulatory or respiratory compromise. Hypotension should be addressed by placement of the patient in a recumbent position, and if necessary, administration of vasopressors and infusions of large volumes of intravenous fluids/colloid to compensate for peripheral vasodilation and for intravascular fluid loss caused by third spacing. Bronchospasm should be treated with an inhaled bronchodilator, theophylline, or both. For patients with life-threatening anaphylaxis who are poorly responsive to initial doses of epinephrine, more frequent or

higher doses may be required. If the patient does not respond to several doses of subcutaneous epinephrine, intravenous administration of epinephrine might be considered. Intravenous epinephrine should be administered either by using a formulation of 1:10,000 (10 μg/ml) epinephrine or by first diluting a 1:1000 (100 μg/ml) dilution (wt/vol) of epinephrine to a 1:10,000 dilution. The infusion of either preparation should initially be titrated at 1 μg/min, which can be increased to 2 to 10 μg/min. These doses may be easier to administer by using a 1:100,000 (1 μg/ml) dilution. For refractory cardiorespiratory arrest in children, the initial intravenous dose is 10 μg (0.01 mg) per kilogram body weight or 0.10 ml of 1:10,000 (wt/vol) dilution. Subsequent

doses are 100 μg/kg (1 ml of 1:10,000) (wt/vol) every 3 to 5 minutes, and if still refractory, the dose may be increased to 200 μg/kg. Patients given intravenous epinephrine require cardiac, respiratory, and blood pressure monitoring.

Annotation 7: Good clinical response?

A good clinical response represents resolution of the reaction. If there is partial resolution or concern about biphasic anaphylaxis, continuous monitoring is suggested. Additional history might reveal previous episodes of anaphylaxis or asthma. Antihistamines may be useful in anaphylaxis particularly for urticaria, angioedema, or both. An H2 receptor antagonist, used with an H1 antihistamine, may be useful in reversing hypotension refractory to epinephrine and intravascular fluid replacement. Corticosteroids (e.g., 200 mg intravenous hydrocortisone) may reduce the risk of recurring or protracted anaphylaxis, although direct clinical evidence for this is sparse. Elevated tryptase levels imply mast cell mediator release and can help differentiate true anaphylaxis from other events. Tryptase levels peak 1 to 2 hours after onset of anaphylaxis and decline with first order kinetics at a half life of around 2 hours.

Annotation 8: Additional treatment

Patients experiencing anaphylaxis may not always respond adequately to one injection of epinephrine. Epinephrine has a rapid onset but a short duration of action. At the same time, mediator release from effector cells (e.g., mast cells and basophils) may be prolonged, producing biphasic or protracted anaphylaxis. Therefore patients who receive epinephrine for the treatment of anaphylaxis may not improve sufficiently or may improve and then relapse. Additional doses of epinephrine may be necessary. If subcutaneous epinephrine is not effective, intravenous administration of epinephrine may be required (see annotation of *Box 6*).

Patients receiving β-adrenergic blocking agents may not respond to epinephrine and may require substantial fluid replacement. Patients receiving β-adrenergic blocking agents who do not respond to epinephrine and fluid replacement may respond to glucagon. Patients receiving ACE inhibitors may be at a greater risk of anaphylaxis. There has been a report of a patient receiving an ACE inhibitor who, after failing to respond to epinephrine, responded to administration of angiotensinamide.

Patients with prominent upper and/or lower respiratory manifestations of anaphylaxis may respond to treatment with inhaled β-agonists. Aerosolized β-agonists may be particularly useful when anaphylaxis is associated with bronchospasm, and is not responding to epinephrine.

If the patient is not responding adequately to epinephrine, life support measures may be needed, and the patient should be transported to a hospital setting. Specific treatment for coexisting medical conditions (e.g., coronary artery disease) may be necessary.

Annotation 9: Monitor patient closely, observation for possible late-phase reaction

Patients experiencing acute anaphylactic episodes may be at risk for late-phase reactions. Thus observation for an extended period may be advisable. For mild anaphylactic reactions, this observation may take place at home; for life-threatening anaphylactic episodes, observation and monitoring in a medically supervised setting is recommended.

Annotation 10: Consultation with allergist/immunologist

After initial treatment of acute anaphylaxis, the patient should be followed-up closely for the possibility of recurrent episodes. Follow-up should include a complete evaluation of the patient's condition and a long-term treatment plan. The allergist/immunologist can obtain a detailed allergy history, coordinate laboratory and allergy testing, evaluate the risks and benefits of therapeutic options, and counsel the patient on avoidance measures.

PATIENTS SHOULD BE CONSIDERED FOR CONSULTATION WITH AN ALLERGIST/IMMUNOLOGIST WHEN:

1. The diagnosis is in doubt 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 management or adherence to treatment.
5. Help is needed in testing for, identifying, or managing IgE-mediated reactions or allergic triggers.
6. The patient is a candidate for immunotherapy.
7. The patient requires daily medications for prevention.
8. The patient needs intensive education regarding avoidance or management.
9. Help is needed in treatment compliance.
10. Help is needed with new or investigative therapy.
11. Goals of treatment have not been met.
12. Anaphylaxis is complicated by a comorbid condition.
13. Anaphylaxis is complicated by psychological factors.
14. The patient has asked for a consultation.

IV. Summary statements

CONSULTATION WITH AN ANAPHYLAXIS SPECIALIST

- Anaphylaxis is a potentially life-threatening condition; recurrences must be prevented if at all possible.
- To maximize the chance of preventing recurrences of anaphylaxis, the etiology should be determined, and the patient should be carefully instructed on measures for avoidance, as well as emergency treatment.
- If future exposure is unavoidable, desensitization or allergen immunotherapy might be considered.
- Consultation and cooperative interaction with the primary care provider, health care providers treating anaphylaxis on an emergent basis, and the allergist-immunologist maximizes the possibility of a successful outcome for the patient and the prevention of subsequent life-threatening episodes.

DEFINITIONS OF ANAPHYLAXIS AND ANAPHYLACTOID EVENTS

- Anaphylaxis is defined as an immediate systemic reaction caused by rapid, IgE-mediated immune release of potent mediators from tissue mast cells and peripheral blood basophils.
- Anaphylactoid reactions are immediate systemic reactions that mimic anaphylaxis but are not caused by IgE-mediated immune responses.
- The temporal occurrence of these reactions is usually immediate but may be delayed depending on the route of exposure. Occasionally, biphasic reactions may occur.

EVALUATION AND MANAGEMENT OF PATIENTS WITH A HISTORY OF ANAPHYLAXIS

- A detailed history is important in the ultimate care of individuals who have had an anaphylactic or anaphylactoid episode.
- Proper timing of laboratory studies, such as blood tests or urine assays, is important in making these studies optimally useful.
- Effective treatment demands early recognition of the event.
- The possibility of anaphylaxis should be considered in any setting where medication or biologics are given, especially by injection.
- Medical facilities should have an established protocol for prompt therapy of anaphylaxis. Supplies that are needed should be promptly available. Oxygen, aqueous epinephrine, injectable antihistamines, intravenous glucocorticosteroids, oropharyngeal airway, and supplies to maintain intravenous fluid therapy are crucial.

- Phone numbers for paramedical rescue squads and ambulance services should be at hand.
- Protocols for the office staff and for patients should be available.

ALLERGENIC EXTRACTS AND IMMUNOTHERAPY

- The risk of fatal and nonfatal systemic reactions after administration of allergenic extract is very low. The risk of such reactions after allergy skin testing is even lower.
- Risk factors for the development of systemic reactions to allergen immunotherapy may include: (1) unstable steroid-dependent asthma; (2) a high level of allergic reactivity based on diagnostic tests (usually immediate hypersensitivity skin tests); (3) a history of previous systemic reactions to allergen immunotherapy; (4) starting a new vial of extract; (5) asthmatic symptoms present immediately before receiving an injection of allergenic extract; (6) concomitant treatment with β-adrenergic blocking agents or ACE inhibitors; (7) administration of pollen extracts; and (8) a rate of increase in the dose of allergenic extract that is too rapid considering the patient's degree of hypersensitivity.
- Careful benefit: risk assessment of patients should be made in regard to performing allergy skin testing and/or initiating allergen immunotherapy.
- Treatment of anaphylaxis resulting from administration of allergenic extracts is essentially the same as the treatment of anaphylaxis from other causes.
- In rare cases of anaphylaxis, onset may be delayed for longer than an hour.

FOODS

- Severe food reactions have been reported to involve the gastrointestinal, cutaneous, ocular, respiratory, and cardiovascular systems.
- The greatest number of anaphylactic episodes in children have involved peanuts, other legumes, true nuts (i.e., walnuts, pecans, and others), fish, shellfish, milk, and eggs. Cross-reactivity with other foods in the same group is unpredictable. Condiments can also cause anaphylaxis.
- Anaphylactic reactions to foods almost always occur immediately. Symptoms may then subside only to recur several hours later.
- The most useful diagnostic tests include skin tests and food challenges. In vitro testing with foods is a safe alternative screening procedure.
- Double- or single-blind placebo-controlled food challenges may be done in patients with suspected food allergy in a medical facility by personnel experienced in performing the procedure and prepared to treat anaphylaxis.

- Patient education about avoidance and management of accidental ingestion is important.
- Schools may 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.

AVIAN-BASED VACCINES

- Adverse reactions to avian-based vaccines have been attributed to the egg protein in the vaccine, as well as to hydrolyzed gelatin, sorbitol, and neomycin in some of the vaccines.
- True anaphylactic reactions to vaccines are rare, including those vaccines with minute quantities of avian protein (measles, mumps, yellow fever, and influenza).
- A careful history should be taken to document the symptoms and severity of prior allergic reactions to egg protein, vaccines, and agents contained in vaccines (e.g., gelatin).
- With a history of exquisite sensitivity (anaphylaxis) to egg protein, the utility of vaccine skin testing to predict vaccine reactions remains controversial. However, it may be considered in this high-risk group, particularly if influenza or yellow fever vaccine are to be administered. If the vaccine skin test response is negative, the vaccine can be given.
- If a positive skin test response to a vaccine is obtained, a desensitization protocol can be used to administer the vaccine, although desensitization is not believed to be necessary by some experts. Adverse reactions have been reported during skin testing and desensitization. Therefore, these procedures should be performed by personnel trained to treat anaphylaxis.

INSECT STINGS AND BITES

- Insects from the Hymenoptera order can cause systemic allergic reactions in sensitized patients.
- Reactions to insect stings may include local, as well as generalized, skin, respiratory, and/or vascular reactions. There are no data that large local reactions predispose patients to systemic reactions.
- Late reactions after insect stings include serum sickness–like syndromes, some of which are not IgE-mediated.
- Immediate hypersensitivity skin testing with venom to honeybee, wasp, yellow jacket, yellow hornet, and white-faced hornet venoms is the most sensitive method for determining specific IgE sensitivity in patients who have had anaphylactic reactions from stings of these insects.
- Skin tests with whole body extract from fire ants and triatoma should be used to document IgE sensitivity in patients with reactions to these types of insects.
- Immunotherapy with Hymenoptera venom for honeybee, yellow jacket, white-faced hornet, yellow

hornet, and wasp venom is extremely efficacious and is recommended for patients with anaphylactic reactions after Hymenoptera stings.
- Immunotherapy with Hymenoptera venom is currently recommended for a period of 3 to 5 years, but the duration of venom immunotherapy should be individualized.
- The imported fire ants (IFAs), *Solenopsis invicta and Solenopsis richteri*, are responsible for significant allergic reactions. The typical result of an IFA sting is the development of a pruritic wheal and flare at the site of the sting within 20 minutes. Six hours later, a pustule forms, which continues to develop for the next 24 hours.
- Systemic reactions to IFA stings exhibit a spectrum that is similar to those reactions after stings of other Hymenoptera species. From 2% to 4% of patients have been reported to have serious systemic anaphylactic reactions after IFA stings.
- The diagnosis of IFA sting reactions includes a history of a typical fire ant mound in the vicinity of the sting incident and the presence of a typical pustule at the sting site. Documentation of specific IgE sensitivity to IFA is usually performed by skin testing with imported fire ant whole body extract (IFA-WBE).
- Skin tests with IFA-WBE extracts are sensitive for determining specific IgE sensitivity in patients who have had a history of generalized systemic anaphylactic reactions. In vitro testing with whole body extract (WBE-RAST) is not as sensitive as testing skin for determining IFA sensitivity.
- Triatoma, indigenous to the southwest, is a nocturnal blood-sucking arthropod whose bite can produce anaphylaxis. Skin testing can be used to confirm the diagnosis, and subsequent reactions can be prevented by allergen immunotherapy. Other biting insects may occasionally cause anaphylaxis.

LATEX

- Latex (rubber) hypersensitivity is a significant medical problem, and three groups are at higher risk of reactions: health care workers, children with spina bifida and genitourinary abnormalities, and workers with occupational exposure to latex.
- To identify IgE-mediated sensitivity, 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. Although a standardized, commercial skin test reagent for latex is not yet available in the United States, many allergy centers have prepared latex extracts for clinical testing. In vitro assays for IgE to latex may also be useful, although these tests are generally less sensitive than skin tests.
- Patients with spina bifida (regardless of a history of latex allergy) and patients with a positive history of latex allergy ideally should have all medical/surgi-

cal/dental procedures performed in a latex-controlled environment.

- A latex-controlled environment is defined as 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.
- 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 may minimize latex sensitization of health care workers and patients and should reduce the risk of inadvertent reactions to latex in previously sensitized individuals.
- Patients with a diagnosis of latex allergy by history or skin testing should wear a medical identification bracelet, carry a medical identification card, or both. If patients have a history of anaphylaxis to latex, it may be important for them to carry epinephrine and antihistamines for self-administration.

β-LACTAM ANTIBIOTICS

- Penicillin is the most frequent cause of anaphylaxis in humans and has been estimated to be responsible for 75% of anaphylactic deaths in the United States.
- Although allergic reactions may occur after administration of penicillin by any route, parenteral administration is most likely to induce severe reactions such as anaphylaxis. Oral administration appears considerably safer.
- Patients with a history of a prior penicillin reaction are six times more likely to experience a reaction on subsequent exposure compared to those without a previous history.
- Over 80% of patients with a history of allergy to penicillin do not have penicillin-specific IgE antibodies as detected by skin testing.
- If a patient requires penicillin and has a past history of penicillin allergy, it is necessary to skin test the patient for the presence of penicillin-specific IgE antibodies before assuming that the patient will not be able to tolerate penicillin.
- Skin testing identifies patients with IgE antibodies specific for penicillin, who, as a result, may be at risk of an immediate reaction if given penicillin.
- Skin testing for penicillin does not predict the later development of IgE-mediated reactions or reactions caused by other immune mechanisms.
- IgE antibodies to minor determinants are most frequently implicated in anaphylactic reactions to penicillin.
- Evaluation by RAST or ELISA testing does not reliably rule out allergy to penicillin because of the insensitivity of the test and the lack of an appropriate minor determinant reagent.

- Patients with a history of possible allergic reaction to penicillin who have a recommended indication for penicillin treatment should be skin tested.
- After anaphylaxis, there is an interval of time during which skin test results may not be reliable. This interval has been reported to vary from 1 to 2 weeks or longer.
- Skin testing is generally not recommended for a patient with a history of an exfoliative dermatitis, Stevens-Johnson syndrome or toxic epidermal necrolysis, caused by penicillin or other β-lactam medications.
- Patients with a positive family history but no personal history of penicillin allergy do not require penicillin skin testing because they are generally not at risk of having an allergic reaction to penicillin.
- If skin test results for penicillin with major (penicilloyl) and minor determinants (penicillin G and others) are negative, 97% to 99% of patients (depending on reagents used) will tolerate penicillin administration without risk of an immediate reaction. By using the above reagents and proper technique by skilled personnel, serious reactions, including anaphylaxis and death, are extremely rare.
- If a patient has a positive history and a positive skin test response to penicillin, there is a 50% or greater chance of an immediate reaction if penicillin is given again.
- If the patient has a past history of an allergic reaction to penicillin and the skin test response is positive to either major or minor determinants, the patient should receive an alternative antibiotic unless the indication for penicillin is clear. If administration of penicillin is mandatory in this setting, desensitization is indicated.
- If the patient has a past history of allergy to penicillin and the skin test response is negative to penicilloyl polylysine and penicillin G, there is a small chance that IgE antibodies to other minor determinants not contained in penicillin G may be present.
- Administration of ampicillin and amoxicillin is associated with the development of morbilliform rashes in 5% to 13% of patients. These patients should not be considered at risk of a life-threatening reaction to penicillin and therefore do not require skin testing. On the other hand, if the rash to ampicillin or amoxicillin is urticarial, or if the patient has a history of anaphylaxis, the patient should undergo penicillin skin testing before a future course of penicillin is given.
- Carbapenems (e.g., imipenem) should be considered cross-reactive with penicillin. Aztreonam, a monobactam, rarely cross-reacts with penicillin.
- Cephalosporins and penicillins have a common β-lactam ring structure, and varying degrees of cross-reactivity have been reported. However, the risk of allergic reactions to cephalosporins in pa-

tients allergic to penicillin appears to be low (less than 10%). First generation cephalosporins may pose a greater risk than second or third generation cephalosporins.

- If a patient has a questionable history of penicillin allergy and requires a cephalosporin, penicillin skin testing can be considered to ensure the absence of penicillin-specific IgE antibodies.
- If there is consideration of cephalosporin use in a patient who has a history of an immediate-type reaction to penicillin, skin testing to major and minor determinants of penicillin should be done to determine if the patient has penicillin-specific IgE antibodies. If the skin test response is negative, the patient can receive a cephalosporin at no greater risk than the general population.
- If there is consideration of cephalosporin use in a patient with a history of penicillin allergy who has a positive skin test response to penicillin, the physician's recommendations may include: (1) administration of an appropriate alternative antibiotic; (2) a cautious graded challenge (test dosing) with appropriate monitoring, recognizing that there is at least a 5% chance of inducing an anaphylactic reaction; or (3) desensitization to the cephalosporin that is proposed for use.
- Patients with a history of an IgE-mediated reaction to a cephalosporin who require penicillin should undergo penicillin skin testing. If the test responses are negative, they can receive penicillin; if positive, they should either receive an alternative medication or undergo desensitization to penicillin.
- If a patient with a past history of allergy to one cephalosporin requires another cephalosporin, skin testing with the required cephalosporin can be done, recognizing that the negative predictive value is unknown. If the skin test response for the cephalosporin is positive, control patients can be tested to determine if the positive response was caused by irritation or was IgE-mediated.

ASA/NSAIDS

- Aspirin (ASA) and nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with a variety of non-IgE-mediated adverse effects. These include systemic reactions, such as rhinoconjunctivitis, bronchospasm, urticaria, angioedema, and laryngeal edema.
- There is no definitive skin or in vitro test to identify patients who are intolerant to ASA or NSAIDs. On the other hand, carefully performed oral ASA/NSAID challenges can be useful in making a more definitive diagnosis.
- Once a diagnosis has been made, avoidance is essential in preventing life-threatening reactions to these agents. This requires educating the patient

about combination products (including over-the-counter medications) containing ASA or NSAIDs.

- Allergy/immunology specialists are frequently asked to clarify the risk of reactions to ASA/NSAIDs and to devise a strategy for dealing with these therapeutic dilemmas.
- It may be useful to refer a patient suspected of being intolerant to ASA or a NSAID to an allergist-immunologist and/or center where oral ASA/NSAID challenges are performed routinely in a well-equipped medical facility, because of the possibility of life-threatening reactions that can occur from such challenges.
- If the ASA/NSAID challenge is positive, pharmacologic desensitization and continued treatment with ASA or NSAIDs can be used if there is a medical indication for this type of medication.

ANAPHYLACTOID REACTIONS TO RADIOGRAPHIC CONTRAST MATERIAL

- Anaphylactoid reactions to radiocontrast material (RCM) can occur after intravascular administration and during hysterosalpingograms, myelograms, and retrograde pyelograms.
- Anaphylactoid reactions to RCM are clinically indistinguishable from IgE-mediated immediate hypersensitivity anaphylactic reactions, although they do not appear to be associated with IgE or any other type of immunologic reaction.
- The treatment of anaphylactoid reactions to RCM is not different than the treatment of anaphylactic reactions caused by allergen-IgE interaction and resultant mast cell–mediator release.
- Patients who have experienced previous anaphylactoid reactions from the administration of radiocontrast material (RCM) are at risk for a repeat reaction. Estimates of this risk range from 16% to 44% for procedures with high osmolality RCM. Therefore the physician should consider other alternatives in managing such patients rather than procedures that require readministration of RCM.
- With pretreatment and the use of lower osmolar RCM, the risk of repeat anaphylactoid reactions is reduced to approximately 1%.
- Pretreatment regimens for prevention of repeat anaphylactoid reactions have consisted of oral glucocorticosteroids, H1 and H2 antihistamines, and other medications such as ephedrine.

INSULIN

- In general, the degree of insulin immunogenicity is in the following order: bovine is greater than porcine, which is greater than human. Although anaphylactic reactions to human insulin produced by recombinant DNA technology are rare, they can occur.

- Insulin-induced anaphylaxis is characterized by the same manifestations as anaphylaxis from other causes.
- Patients are more likely to experience anaphylaxis from insulin administration if therapy is interrupted.
- Skin testing with insulin can aid in making the diagnosis of insulin-induced anaphylaxis. In addition, skin testing can be used to select the least allergenic insulin for administration to patients who have a history of immediate hypersensitivity reactions to insulin, yet require insulin.
- Patients with a history of anaphylaxis to insulin can be desensitized to insulin if no alternative medications exist to treat their disease.

PROTAMINE

- Intravenous administration of protamine, a polycationic protein used to reverse heparin anticoagulation, may cause anaphylaxis, as well as transient elevations in pulmonary artery pressure and/or cardiovascular collapse.
- The pathogenesis of these acute reactions has not been proven, but both nonimmune and immune (IgE) mechanisms have been reported.
- Patients who previously required protamine-containing insulin or intravenous protamine are at significantly increased risk for having anaphylaxis and other adverse reactions from intravenous protamine.
- Although intracutaneous tests with protamine may be helpful in identifying a possible IgE-mediated response in selected cases, these tests must be interpreted with caution because they do not necessarily predict clinical sensitivity and do not identify all patients at risk.
- A variety of alternative approaches may be considered to avoid the need for protamine reversal of heparinization. Several alternative agents may be used for heparin reversal, but these are not readily available on an emergency basis. For patients at high risk for protamine reactions, one should attempt to obtain one of the alternative reversal agents prior to the procedure that requires heparin anticoagulation.
- Although premedication with antihistamines and corticosteroids may be considered in an effort to reduce protamine reactions, there are no controlled trials that have demonstrated that premedication is effective in this setting.

LOCAL ANESTHETICS

- Anaphylactic reactions to local anesthetics or constituents of local anesthetics have been reported, although IgE-mediated systemic anaphylaxis to these agents is rare.
- Local anesthetics are classified into groups, including esters (aminobenzoate and benzoic acid subtypes), amides, ethers, and ketones.

- Provocative (graded) dose challenge should be considered when the cause of a reaction is unknown or proof of safety is required before administration.
- Reactions to additives such as parabens or sulfites may occur but are rare, and routine testing with these substances is not recommended.
- In patients who have had reactions to an ester-type local anesthetic, an amide should be considered for provocative (graded) dose testing. If the patient had a reaction to an amide, another amide might be considered because cross-reactivity among amides has not been documented.

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

- The incidence of generalized anaphylactic reactions 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.
- It may be difficult to differentiate between immune and nonimmune mast cell–mediated reactions and pharmacologic effects from the variety of medications administered during general anesthesia.
- Thiopental allergy has been documented by skin tests.
- Neuromuscular blocking agents, such as succinylcholine, can cause nonimmunologic histamine release, but there have been reports of IgE-mediated mechanisms in some cases.
- Reactions to opioid analgesics are usually caused by direct mast cell–mediator release rather than IgE-dependent mechanisms.
- Antibiotics that are administered perioperatively can cause immunologic or nonimmunologic generalized reactions.
- Protamine can also cause severe systemic reactions through IgE-mediated or nonimmunologic mechanisms.
- Latex is a potent allergen, and IgE-mediated reactions to latex during anesthesia have been clearly documented. Patients with multiple surgical procedures (e.g., 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.
- Ethylene oxide anaphylactic reactions have been reported particularly in patients who have exposure to hemodialysis or who are undergoing plasmapheresis.
- Blood transfusions can elicit a variety of systemic reactions, some of which may be IgE-mediated or mediated through other immunologic mechanisms.

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

PROGESTERONE

- Unexplained episodes of anaphylaxis may be caused by unusual reactivity to progesterone. Anaphylactic symptoms tend to be premenstrual but may occur anytime during the menstrual cycle. In one report, lactation caused complete remission of symptoms.
- The pathogenesis of this disorder is unknown, but laboratory studies have shown that progesterone may either induce histamine release from basophils directly or make mast cells more susceptible to other mast cell degranulators.
- Treatment options include a leutinizing hormone-releasing hormone (LHRH) agonist analog (e.g., Naferelin) or oophorectomy in particularly resistant cases.
- A differential consideration that may be confused with progesterone-induced anaphylaxis is catemenial anaphylaxis, which is not related to progesterone reactivity. Anaphylactic symptoms occur during menses, and full recovery after oophorectomy has been reported.

ANAPHYLACTOID REACTIONS TO INTRAVENOUS FLUORESCEIN

- Anaphylactoid reactions may occur after intravenous administration of fluorescein, a yellow, water-soluble, dibasic xanthine dye used in the diagnosis and detection of chorioretinal lesions.
- The most common adverse reactions to intravenous fluorescein are nausea and vomiting, but anaphylactoid reactions resulting in death have also been reported. Although increase in plasma histamine and decrease in various complement components have been described after anaphylactoid reactions, the pathogenesis of these reactions is not known.
- Prophylactic regimens similar to those used for radiocontrast media should be considered in patients who have had a previous anaphylactoid reaction and in whom use of intravenous fluorescein dye is indicated. However, these have not been used in sufficient numbers of patients to provide a definitive recommendation.

SEMINAL FLUID

- Anaphylaxis caused by human seminal fluid has been shown to be due to IgE-mediated sensitization by proteins of varying molecular weight.

- 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 period.
- The diagnosis is confirmed by either skin or in vitro tests for serum-specific IgE, with proper reagents obtained from fractionation of seminal fluid components.
- Prevention of reactions to seminal fluid can be accomplished by use of barrier condoms.
- 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.

EXERCISE-INDUCED ANAPHYLAXIS

- Exercise-induced anaphylaxis is a unique form of physical allergy. Initial symptoms typically include fatigue, diffuse warmth, pruritus, erythema, and urticaria, with progression to angioedema, gastrointestinal symptoms, laryngeal edema, and/or vascular collapse.
- Factors that have been associated with exercise-induced anaphylaxis include medications, (e.g., aspirin/other nonsteroidal antiinflammatory agents) or food ingestion before exercise.
- Patients with exercise-induced anaphylaxis may have a higher incidence of personal and/or family history of atopy.
- Exercise-induced anaphylaxis should be distinguished from other exercise-associated syndromes, such as cholinergic urticaria and exercise-induced asthma.
- Medications used prophylactically are generally not useful in preventing exercise-induced anaphylaxis.
- Exercise should be discontinued at the onset of symptoms of exercise-induced anaphylaxis, and for some patients, exercise should be avoided in the immediate postprandial period (4 to 6 hours after eating).
- The emergency management of exercise-induced anaphylaxis is the same as the treatment of anaphylaxis from other causes.
- Patients with exercise-induced anaphylaxis should carry epinephrine and ideally should wear and/or carry Medic Alert identification denoting their condition.

IDIOPATHIC ANAPHYLAXIS

- Patients who have idiopathic anaphylaxis present with the same constellation of symptoms that are seen in other types of anaphylactic/anaphylactoid reactions.
- Patients with idiopathic anaphylaxis should receive intensive evaluation, including a meticulous history,

with careful analysis of events surrounding the development of episodes of anaphylaxis.

- Clinical evaluation may indicate the need for specific laboratory studies, which may help to exclude an underlying systemic disorder (e.g., systemic mast cell disease or hereditary angioneurotic edema). Selective testing for specific IgE antibodies and carefully controlled challenge procedures may occasionally help to establish an etiology for recurrent episodes of anaphylaxis.

- The acute treatment of idiopathic anaphylaxis is the same as the treatment of other types of anaphylactic/anaphylactoid reactions. Various protocols have been developed for the prevention of idiopathic anaphylaxis, but the treatment (e.g., corticosteroids, β-agonists, and antihistamines) often requires individualization.

- Education and support of patients with idiopathic anaphylaxis is an essential part of the management program.

PREVENTION OF ANAPHYLAXIS

- Major risk factors for recurrence of anaphylaxis include a prior history of such reactions, β-adrenergic blocker or possibly ACE inhibitor therapy, and the multiple antibiotic sensitivity syndrome. Atopic background may be a risk factor for venom- and latex-induced anaphylaxis and possibly anaphylactoid reactions to radiographic contrast material but not for anaphylactic reactions to many medications.

- 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.

- Avoidance management should be individualized, taking into consideration factors such as age, activity, occupation, hobbies, residential conditions, access to medical care, and the patient's level of anxiety.

- Pharmacologic prophylaxis can be utilized to prevent recurrent anaphylactoid reactions to radiographic contrast material and to fluorescein, as well as to prevent idiopathic anaphylaxis. Pretreatment with glucocorticosteroids and antihistamines markedly reduces the occurrence of subsequent reactions.

- 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.

- 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. Oral graded challenge to medications such as aspirin, sulfasalazine, or allopurinol may restore drug tolerance as long as the medication is administered on a continuous basis.

- Patient education may be the most important preventive strategy. Patients must 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.

V. Consultation with an anaphylaxis specialist

SUMMARY STATEMENTS

- Anaphylaxis is a potentially life-threatening condition; recurrences must be prevented if at all possible.
- To maximize the chance of preventing recurrences of anaphylaxis, the etiology should be determined, and the patient should be carefully instructed on measures for avoidance, as well as emergency treatment.
- If future exposure is unavoidable, desensitization or allergen immunotherapy might be considered.
- Consultation and cooperative interaction with the primary care provider, health care providers treating anaphylaxis on an emergent basis, and the allergist-immunologist maximizes the possibility of a successful outcome for the patient and the prevention of subsequent life-threatening episodes.

Anaphylaxis is a potentially life-threatening condition, recurrence of which must be prevented if at all possible.

Cooperative interaction among the patient and/or the patient's representative, the primary care physician/provider, and the allergist-immunologist is necessary to maximize the possibility of preventing recurrences.

It is important that the primary care physician/provider recognize the contribution that can be made by the allergist-immunologist in the diagnosis and management of anaphylaxis and anaphylactoid reactions. In addition, physicians treating anaphylaxis on an emergent basis also must be aware of the essential role of the allergist-immunologist in the management of these reactions and the need for follow-up to identify the causative agent.

The allergist-immunologist should recognize the importance of the primary care provider in the process of recognition and referral of patients with anaphylaxis and anaphylactoid reactions, as well as the role of the primary care provider in the prevention of further episodes.

Active involvement of the allergist-immunologist in identifying the causative agent, educating the patient in measures of avoidance, and providing emergency treatment and possible allergen immunotherapy or desensitization would be expected to lower the cost of subsequent health care, as well as decrease morbidity and mortality from anaphylaxis.

There are strong reasons for recommending that a patient consult an allergist-immunologist as soon as an anaphylactic or anaphylactoid reaction is suspected. Such reactions should be suspected if the patient is first seen with a history of any one or more of the following: cutaneous manifestations, including pruritus, flushing, diffuse urticaria, and angioedema; vascular collapse; respiratory difficulty; gastrointestinal symptoms or cardiac symptoms that occur rapidly after exposure to a triggering agent. Inclusion of the allergist-immunologist is of particular importance when the triggering agent is not obvious.

Identification of the causative agent is essential. Possibilities may include any one or more of the following:

- medications, including, but not limited to, antibiotics, aspirin, nonsteroidal antiinflammatory agents, local and general anesthetics, insulin, protamine, and progesterone;
- vaccines, especially egg-based vaccines;
- blood components or biologic fluids (e.g., gamma globulin or seminal fluid);
- diagnostic testing material (e.g., radiographic contrast material);
- foods;
- insect bites and stings;
- latex;
- allergenic extracts.

Other triggers, which may be less easy to identify, include exercise and physical factors, such as cold and sunlight. Idiopathic anaphylaxis is a diagnosis of exclusion, for which the allergist-immunologist is best trained to confirm the diagnosis. Once the precipitating factor is identified through an investigative history along with appropriate testing, the allergist-immunologist should be able to educate the patient regarding prevention, emergency treatment measures, and the possible role of immunotherapy.

The allergist-immunologist ordinarily should provide the primary care provider with information regarding the identification of the causative agent and precautions to follow (including the potential adverse effect on treatment from the use of medications, such as β-adrenergic blocking agents, ACE inhibitors, or monoamine oxidase inhibitors) and make recommendations regarding treatment and/or desensitization if necessary. Consultation and interaction between the primary care provider, as well as other physicians treating anaphylaxis on an emergent basis, and the allergist-immunologist is essential to maximize the chance of achieving optimal outcomes.

Patients should be considered for consultation with an allergist-immunologist when any of the following occur:

1. The diagnosis is in doubt 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 management or adherence to treatment.
5. Help is needed in testing for, identifying, or managing IgE-mediated reactions or allergic triggers.
6. The patient is a candidate for immunotherapy.
7. The patient requires daily medications for prevention.

8. The patient needs intensive education regarding avoidance or management.
9. Help is needed in treatment compliance.
10. Help is needed with new or investigative therapy.

11. Goals of treatment have not been met.
12. Anaphylaxis is complicated by a comorbid condition.
13. Anaphylaxis is complicated by psychologic factors.
14. The patient has asked for a consultation.

VI. Definitions of anaphylaxis and anaphylactoid events

SUMMARY STATEMENTS

- Anaphylaxis is defined as an immediate systemic reaction caused by rapid, IgE-mediated immune release of potent mediators from tissue mast cells and peripheral blood basophils.
- Anaphylactoid reactions are immediate systemic reactions that mimic anaphylaxis but are not caused by IgE-mediated immune responses.
- The temporal occurrence of these reactions is usually immediate but may be delayed depending on the route of exposure. Occasionally, biphasic reactions may occur.

The term *anaphylaxis* refers to a systemic immediate hypersensitivity reaction caused by the rapid, IgE-mediated immune release of potent mediators from tissue mast cells and peripheral blood basophils. The term *anaphylactoid* refers to those clinical events caused by mediator release from mast cells and basophils by non-IgE-mediated triggering events.[1,2] These events are potentially life-threatening reactions, although some are self-limited without treatment.

Clinically, the term anaphylaxis is most often used to describe rapidly developing generalized reactions that include pruritus, urticaria, angioedema (especially laryngeal edema), hypotension, wheezing and bronchospasm, nausea, vomiting, abdominal pain, diarrhea, uterine contractions, and/or direct cardiac effects, including arrhythmias.[3] These clinical manifestations can occur singly or in various combinations and usually occur within moments of exposure. However, signs and symptoms may begin 30 to 60 minutes after exposure, and in some cases onset may be delayed for longer than an hour. Signs and symptoms can be protracted and variably responsive to treatment. Biphasic anaphylaxis can also occur. In this situation, the early signs and symptoms clear (either spontaneously or after acute therapy) and reappear several hours later. Generally, the severity of an anaphylactic event will relate to the suddenness of its onset. Although the magnitude of the event also relates to the size of the challenge (i.e., the bigger the provocative dose, the more severe the reaction will be), severe reactions can occur after exposure to minute amounts of allergen in highly sensitive patients.[1,2] Anaphylactoid reactions generally are dependent on systemic exposure to provoking agents and usually in amounts greater than would be expected to elicit anaphylaxis.

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VII. Evaluation and management of patients with a history of anaphylaxis

SUMMARY STATEMENTS

- A detailed history is important in the ultimate care of individuals who have had an anaphylactic or anaphylactoid episode.
- Proper timing of laboratory studies, such as blood tests or urine assays, is important in making these studies optimally useful.
- Effective treatment demands early recognition of the event.
- The possibility of anaphylaxis should be considered in any setting in which medication or biologics are given, especially by injection.
- Medical facilities should have an established protocol for prompt therapy of anaphylaxis. Supplies that are needed should be promptly available. Oxygen, aqueous epinephrine, injectable antihistamines, intravenous glucocorticosteroids, oropharyngeal airway, and supplies to maintain intravenous fluid therapy are crucial.
- Phone numbers for paramedical rescue squads and ambulance services should be at hand.
- Protocols for the office staff and for patients should be available.

All individuals who have had a known or suspected anaphylactic episode require a careful allergy evaluation. The management goals are to prevent or minimize the risk of future anaphylactic episodes by determining the etiologic agent, to educate the patient and/or family members regarding avoidance of that agent, and to provide appropriate treatment of possible future reactions.

CLINICAL HISTORY

The history is crucial in determining the nature of the clinical event, in helping to construct and analyze a differential diagnosis, and in identifying a specific cause of anaphylaxis. There are two important questions regarding the possible etiology of the event: (1) Is the clinical event indicative of an anaphylactic reaction, or an alternative event? (2) Is there a possible cause-and-effect relationship between the reaction and an identifiable agent?

Because most anaphylactic reactions occur rapidly after contact with the allergen, the history should concentrate on possible causative agents immediately before the event. Information from family members, friends, or others can be helpful and is especially important if there is loss of consciousness during the reaction. Information from medical personnel who treated the patient, including documentation of the exact clinical manifestations of the reaction, vital signs, treatment

given, and response to treatment, are important. Each separate episode of anaphylaxis in patients with recurrent events should be assessed thoroughly.

TREATMENT OF ANAPHYLAXIS AND ANAPHYLACTOID EVENTS

The treatment of these events requires speedy recognition and implementation of proper therapy. The signs and symptoms may vary from mild to severe.[1] Symptoms usually begin within minutes of exposure to a causative agent and frequently progress in an explosive manner. A common initial presentation includes a sense of impending doom, generalized warmth or flush with tingling or pruritus of the skin, especially of the palms of the hands and/or soles of the feet, as well as of the lips and the genital area. Complaints of a lump in the throat, throat tightness, hoarseness or difficulty in swallowing, inspiratory stridor, chest tightness, wheezing, or shortness of breath should alert the medical team to the possible presence of an emergency and should result in immediate evaluation and implementation of an emergency plan for the management of anaphylaxis.

Other symptoms of anaphylaxis/anaphylactoid reaction that call for immediate assessment and, if appropriate, implementation of therapy include cardiovascular symptoms (lightheadedness, faintness, syncope, and palpitations), abdominal symptoms (bloating, nausea, vomiting, and cramps), and upper respiratory symptoms (nasal congestion, rhinorrhea, and sneezing).

In one large series of fatal anaphylactic reactions, 70% of the deaths were from respiratory causes, and 24% were from cardiovascular causes.[2] Death may occur within minutes of the onset of symptoms. Therefore, one may occasionally have to err on the side of providing therapy before one is certain that anaphylaxis is present. In general, the later the symptoms begin after exposure to a causative agent, the less severe the reaction.[3]

PHYSICAL FINDINGS

Physical findings may include flushing; urticaria; swelling of the lips, tongue, uvula, or other areas; expiratory wheezing and/or inspiratory stridor; cyanosis; and hypotension. It is particularly important for the physician to immediately assess the cardiac and respiratory systems for the presence of airway obstruction, bronchospasm, or shock.

Anaphylaxis in the office setting almost always occurs after the administration of an injection of a drug or biologic, most often occurring after the administration of allergenic extracts, chemotherapeutic agents, and antibiotics.

EQUIPMENT

The following equipment and reagents should be available in the office setting for treatment of anaphylaxis when allergen immunotherapy is administered and is also desirable in offices where other drugs or biologics are administered by injection[4]: (1) a stethoscope and sphygmomanometer; (2) tourniquets, syringes, hypodermic needles, and large-bore (14 gauge) needles (smaller for pediatric patients); (3) aqueous epinephrine HCl 1:1000; (4) oxygen and equipment for administration; (5) intravenous fluids and equipment for administration; (6) an oral airway; (7) diphenhydramine; (8) bronchodilator medications for administration by the intravenous or inhaled routes; (9) corticosteroids for intravenous injection; and (10) vasopressors. The availability of an H2 antihistamine for intravenous injection may also be desirable.

It is generally felt that the proper use of the above-listed equipment/medications by appropriately trained personnel should provide effective initial treatment for most, if not all, acute anaphylactic reactions occurring in the office setting.[5]

LABORATORY STUDIES

IgE antibodies to a suspected allergen may be demonstrated by skin tests or by immunoassays. Appropriate skin tests are the diagnostic methods of choice in cases of anaphylaxis to venom from stinging insects or penicillin. Anaphylactoid reactions, by definition, occur independently of IgE antibody and therefore are not able to be evaluated by skin testing or immunoassay.

Laboratory evaluation can be helpful in making the diagnosis of anaphylaxis or distinguishing it from other entities. If carcinoid syndrome or pheochromocytoma is considered, blood levels of serotonin (5-hydroxytryptamine), urinary 5-hydroxyindole acetic acid (5-HIAA), catecholamines, and vanillylmandelic acid can be assessed. If a patient is seen shortly after an anaphylactic episode, plasma and urinary histamine (or histamine metabolites) or serum tryptase determinations could be helpful. Plasma histamine levels are maximal at 10 to 15 minutes and return to baseline by 30 to 60 minutes. Use of plasma histamine levels is clinically problematic because blood specimens must be processed immediately to prevent spontaneous basophil histamine release and the resulting artifactually elevated histamine levels in unseparated blood. Urinary histamine and its metabolites are elevated for a longer duration of time, and measurements of them may be useful.[6]

β-tryptase is a neutral protease stored in mast cell secretory granules that is secreted by human mast cells. Levels in normal blood are undetectable (< 1 ng/ml). Elevated serum levels demonstrate that mast cell activation with mediator release has occurred whether triggered by IgE-mediated anaphylaxis or non-IgE-mediated anaphylactoid reactions. The greater the severity of anaphylaxis, the more likely that serum β-tryptase levels will be elevated. Tryptase levels during food-induced anaphylaxis are less likely to be elevated than during some other forms of anaphylaxis. Absence of elevated tryptase levels does not rule out anaphylaxis by nonmast cell–dependent mechanisms. Serum tryptase is not elevated in some anaphylactoid reactions in which mast cell activation does not occur (e.g., complement activation). Serum β-tryptase levels peak 1 to 2 hours after onset of anaphylaxis and then decline under apparent first order kinetics with a half-life of about 2 hours. Elevated β-tryptase levels may be useful in differentiating anaphylaxis from other events having similar clinical manifestations,[7] particularly if hypotension is present. The best time to obtain serum tryptase levels is between 1 to 2 hours after onset of symptoms, but depending on the maximal level of tryptase, elevated levels may occasionally be detected 6 to 12 hours after an episode.[8] Once a serum sample has been drawn, β-tryptase is fairly stable, and decay occurs more slowly than in vivo, making it possible to sometimes detect elevated tryptase levels in serum stored at room temperature for days to weeks and in frozen serum for months to years. Therefore, if stored serum samples collected at an appropriate time frame are available, consideration may be given to ordering tryptase levels retrospectively 1 or 2 days after an event suspected to cause anaphylaxis. Postmortem serum samples obtained shortly after a subject's death have been successfully assayed for tryptase to support a diagnosis of anaphylaxis as the cause of death.[9]

Unlike β-tryptase, α-tryptase is not stored in secretory granules of mast cells and is released from mast cells in small amounts (normal levels in blood range from 1 to 10 ng/ml). In systemic mastocytosis there is a baseline increase in α-tryptase production. The tryptase that is now commercially available detects both α- and β-tryptase and has a normal range of less than 11 ng/ml. This assay uses a different monoclonal antibody (B12) than the G5 monoclonal antibody used in the tryptase assay that had been generally available in the early 1990s, which primarily detects β-tryptase. For a single serum sample obtained after mast cell dependent systemic anaphylaxis, it appears that the total tryptase assay using B12 is less sensitive than the β-tryptase assay with G5 for detecting elevated tryptase levels. However, if baseline and acute blood samples are compared, a twofold or greater increase in total tryptase during the acute event will provide at least as high a sensitivity as the β-tryptase specific assay.

It may also be helpful to obtain samples of undigested portions of food from emesis because these might be useful for demonstrating specific IgE antibodies to foods.

Once the diagnosis of anaphylaxis is established, it should be recognized that the specific agent may be identifiable.[10] The search for such an agent should include, when appropriate, tests for food allergies.[11, 12] Such tests have been reported to identify the offending agent in some cases previously designated as idiopathic.[13]

Provocative challenge tests, such as deliberate insect sting challenges or oral challenge feedings with foods,[14]

may be necessary to evaluate certain patients. These challenges are not without danger, however, and should be conducted only in facilities with appropriate resuscitation equipment and trained personnel. Recurrent episodes of anaphylaxis in food-sensitive persons may be due to unrecognized contamination of nonallergenic foods by allergenic foods. Uneaten portions of foods suspected of causing reactions can be tested for hidden allergens by inhibition immunoassay with the patients's serum as a source of IgE antibody.

MANAGEMENT OF ANAPHYLAXIS

Prevention of anaphylaxis should be the ultimate goal because it would obviate the need for treatment. For example, individuals with known food allergies should be taught how to interpret the ingredient listings of prepared foods. Most severe food-induced anaphylactic reactions occur outside the home, where sensitized individuals are less likely to be certain of the ingredients in the food consumed.[15]

Every office administering agents from which the development of anaphylaxis could reasonably be expected should have the previously discussed equipment readily available and an established protocol for the management of anaphylaxis. Treatment should be tailored to the severity of anaphylactic reaction.

The following is a sample strategy that can be modified as necessary.[14, 5]

1. Diagnose the presence or likely presence of anaphylaxis.
2. Place patient in recumbent position and elevate lower extremities.
3. Monitor vital signs frequently (every 2 to 5 minutes) and stay with the patient.
4. Administer 1:1000 epinephrine wt/vol (weight/volume) (dose: for adults, 0.01 ml/kg up to a maximum dose of 0.2 to 0.5 ml every 10 to 15 minutes as needed; for children, 0.01 ml/kg/dose to a maximum dose of 0.2 to 0.5 ml) by subcutaneous or intramuscular route, and if necessary, repeat every 15 minutes, up to two doses.
5. Administer oxygen, usually 8 to 10 L/min; lower concentrations may be appropriate in patients with chronic obstructive pulmonary disease.
6. Maintain airway with an oropharyngeal airway device.
7. Administer antihistamine: 25 to 50 mg diphenhydramine (1.0 to 2.0 mg/kg in children), usually given parenterally.
8. If anaphylaxis is due to an injection, administer aqueous epinephrine 0.15 to 0.3 ml into injection site to inhibit further absorption of the injected substance.
9. If hypotension is present or bronchospasm persists in an ambulatory setting, transfer to hospital emergency department by ambulance is appropriate.
10. Treat hypotension with intravenous fluids or colloid replacement and consider use of a vasopressor (e.g., dopamine).

11. Treat bronchospasm, preferably with a β_2-agonist given intermittently or continuously; consider the use of 5.6 mg/kg aminophylline as an intravenous loading dose given over 20 minutes or to maintain a blood level of 8 to 15 μg/ml.
12. Give 5 mg/kg hydrocortisone (or approximately 250 mg) intravenously (20 mg prednisone orally can be given in mild cases). The rationale is to reduce the risk of recurring or protracted anaphylaxis. These doses can be repeated every 6 hours as required.
13. In refractory cases not responding to epinephrine because a β-adrenergic blocking agent is complicating management, 1 mg glucagon given intravenously as a bolus may be useful. A continuous infusion of 1 to 5 mg glucagon per hour may be given if required.
14. In patients receiving a β-adrenergic blocking agent who do not respond to epinephrine, glucagon, intravenous fluids, and other therapy, a risk/benefit assessment may rarely include the use of isoproterenol (a β-agonist with no α-agonist properties). Although isoproterenol may be able to overcome depression of myocardial contractility caused by β-blockers, it may also aggravate hypotension by inducing peripheral vasodilation and may induce cardiac arrhythmias and myocardial necrosis. If a decision is made to administer isoproterenol intravenously, the proper dose is 1 mg in 500 ml D5W titrated at 0.1 mg/kg/min. This can be doubled every 15 minutes. Adults should be given approximately 50% of this dose initially. Cardiac monitoring is necessary, and isoproterenol should be given cautiously when the heart rate exceeds 150 to 189 beats per minute.
15. Medical offices in which the occurrence of anaphylaxis is likely should consider periodic anaphylaxis drills.
16. Protocols for use in schools to manage children at risk for anaphylaxis are available through the *Food Allergy Network*. These protocols include materials for educating teachers, office workers, and kitchen staff in the prevention and treatment of anaphylaxis. Furthermore, patients should be given a handout with suggested strategies for their own care.

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VIII. Allergenic extracts and immunotherapy

SUMMARY STATEMENTS

- The risk of fatal and nonfatal systemic reactions after administration of allergenic extracts is very low. The risk of such reactions after allergy skin testing is even lower.
- Risk factors for the development of systemic reactions to allergen immunotherapy may include: (1) unstable steroid-dependent asthma; (2) a high level of allergic reactivity based on diagnostic tests, usually immediate hypersensitivity skin tests; (3) a history of previous systemic reactions to allergen immunotherapy; (4) starting a new vial of extract; (5) asthmatic symptoms present immediately before receiving an injection of allergenic extract; (6) concomitant treatment with β-adrenergic blocking agents or ACE inhibitors; (7) administration of pollen extracts; and (8) a rate of increase in the dose of allergenic extract that is too rapid considering the patient's degree of hypersensitivity.
- Careful benefit: risk assessment of patients should be made in regard to performing allergy skin testing and/or initiating allergen immunotherapy.
- Treatment of anaphylaxis resulting from administration of allergenic extracts is essentially the same as the treatment of anaphylaxis from other causes.
- In rare cases of anaphylaxis, onset may be delayed for longer than an hour.

It has been estimated that there are 7 to 10 million injections of allergenic extract given per year in the United States. The number of persons receiving allergen immunotherapy is therefore substantial. The number of individuals who undergo skin testing in this country is also significant.

There have been several published studies that have assessed the prevalence of fatal and nonfatal systemic reactions to skin testing and allergen immunotherapy. One such study reported six cases of fatal anaphylaxis from skin testing and 24 cases of fatal anaphylaxis from allergen immunotherapy in a retrospective survey of allergists between 1945 and 1984.[1] In a second survey from 1985 through 1989, there were 17 deaths from allergen immunotherapy and none from skin testing.[2]

Specific allergenic extracts are required for skin testing and allergen immunotherapy. Most of these extracts are not standardized. Extracts that are not standardized are usually labeled by either their protein content per milliliter (PNUs) or in weight per volume units. Neither of these labels of concentration necessarily relate to the biologic potency *(allergenicity)* of the extract. Therefore, a safe and effective dose of a single lot of nonstandardized allergen cannot be generalized to another lot of the same nonstandardized product. Furthermore, it is not clear that different manufacturers of allergenic extracts use similar raw materials or processing methods to produce extracts that may be identically labeled. Thus there is the potential for increased systemic reactions when transferring immunotherapy from one medical facility to another without reassessing the patient's sensitivity with regard to allergenic materials that will be used for future immunotherapy in the new treatment center. Theoretically, there is less risk of adverse reactions with standardized allergens because of greater predictability about their potency.[3]

Risk factors that have been described for the development of systemic reactions to allergen immunotherapy include: (1) unstable glucocorticosteroid-dependent asthma; (2) a high level of allergic reactivity based on diagnostic tests, usually immediate hypersensitivity skin tests; (3) a history of previous systemic reactions to allergen immunotherapy; (4) starting a new vial of extract; (5) asthmatic symptoms present immediately before receiving an injection of allergenic extract; (6) concomitant treatment with β-adrenergic blocking agents; (7) administration of pollen extracts, which may be especially true during high environmental exposure periods to aeroallergens; and (8) a rate of increase in the dose of allergenic extract that is too rapid considering the patient's degree of sensitivity.[1,2] In addition, although not documented in the literature, there is a general feeling that patients with increased allergic symptoms, fever, or an upper respiratory tract infection at the time of administration of allergenic extracts may also be at increased risk of having anaphylactic reactions.

To minimize the chance of patients having anaphylactic reactions to skin testing and allergen immunotherapy, the following measures should be taken:

1. A careful assessment should be made about the need for skin testing. If skin testing is indicated, skin prick testing should generally be performed before intracutaneous testing is done.
2. A careful assessment should be made in regard to the benefits and risks of initiating allergen immunotherapy. Special consideration in this regard should be given to patients who may be at greater risk for anaphylaxis (see above).
3. Allergen immunotherapy should be administered under the supervision of an appropriately trained physician and qualified medical personnel with ready access to emergency equipment. The health care physician who administers immunotherapy injections should be able to recognize early symptoms and signs of anaphylaxis and administer emergency medications if necessary. Qualified medical personnel should be immediately available, know how to adjust dosage, know how to recognize and treat systemic reactions, and have expertise in cardiopulmonary resuscitation.

4. All patients who have received an injection of allergenic extract should be observed for at least 20 minutes after the injection is given, with inspection of the injection site before leaving. Patients should be evaluated before the next immunotherapy injection with regard to local reactions or systemic symptoms occurring later than 20 to 30 minutes after the injection. To do this effectively, education of the patient is essential.

5. The interval between injections of allergenic extract must be evaluated carefully, with consideration given to reduction in dose if it has been longer than the scheduled time between injections.

6. Adjustment of the extract dosage should be made if symptoms of anaphylaxis occur.

7. It may be necessary to adjust the extract dosage if large local reactions occur.

8. More dilute initial extracts should be used in selected patients who appear to have increased sensitivity on the basis of history and/or skin test results for specific IgE antibodies.

9. Patients must be assessed in regard to their general medical condition at the time of the injection (e.g., an upper respiratory tract infection or asthma exacerbation. For more detailed recommendations regarding the prevention and treatment of anaphylaxis in asthmatic patients receiving immunotherapy, see the Practice Parameters for the Diagnosis and Treatment of Asthma, Sections on Asthma and Anaphylaxis and Immunotherapy in the Asthmatic Patient).

10. Procedures should be taken to avoid clerical or nursing errors.

The treatment of anaphylaxis caused by administration of allergenic extracts is essentially the same as the treatment of anaphylaxis caused by other agents. However, treatment of anaphylaxis from administration of allergenic extracts in patients who are receiving β-adrenergic blocking agents concomitantly may require more prolonged and vigorous treatment. This may include substantial fluid replacement and administration of vasopressors because of loss of intravascular fluid volume during anaphylaxis. If such patients do not respond to repeated doses of epinephrine, 1 mg glucagon intravenously can be given as a bolus followed by a 1 to 5 mg/hour infusion. Glucagon causes bronchodilatation and reverses anaphylaxis by increasing intracellular cAMP and release of catacholimies.

In addition, there are data to indicate that patients receiving ACE inhibitors may be at increased risk for development of anaphylaxis, as well as being more refractory to treatment with epinephrine if anaphylaxis develops.[4] This database includes reports from France indicating that the relative risk of anaphylactoid reactions was at least 20 times higher in patients undergoing dialysis if they were receiving ACE inhibitors.[5, 6] It also includes reports from Germany describing patients with stinging insect hypersensitivity taking ACE inhibitors and receiving venom immunotherapy who had recurrent anaphylaxis either from immunotherapy or from sting provocation. These patients had significantly lower renin, angiotensinogen, angiotensin I, and angiotensin II levels than patients who did not have repeated episodes of anaphylaxis with immunotherapy or stings.[7-10]

Because of the possibility of late onset anaphylactic reactions, the patient may follow up for an extended period of time.

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IX. Foods

SUMMARY STATEMENTS

- Severe food reactions have been reported to involve the gastrointestinal, cutaneous, ocular, respiratory, and cardiovascular systems.
- The greatest number of anaphylactic episodes in children have involved peanuts, other legumes, true nuts (i.e., walnuts, pecans, and others), fish, shellfish, milk, and eggs. Cross-reactivity with other foods in the same group is unpredictable. Condiments can also cause anaphylaxis.
- Anaphylactic reactions to foods almost always occur immediately. Symptoms may then subside only to recur several hours later.
- The most useful diagnostic tests include skin tests and food challenges. In vitro testing with foods is a safe alternative screening procedure.
- Double- or single-blind placebo-controlled food challenges may be done in patients with suspected food allergy in a medical facility by personnel experienced in performing the procedure and prepared to treat anaphylaxis.
- Patient education about avoidance and management of accidental ingestion is important.
- Schools may 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.

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.[1]

Severe adverse food reactions have been reported to involve several major systems. Gastrointestinal signs and symptoms include nausea, bloating, diarrhea, and severe abdominal pain. It should be noted that in some females, abdominal pain involves the lowest portion of the abdomen and may be described as a feeling of uterine contractions. Cutaneous manifestations have included angioedema and erythema with or without urticaria. The ocular presentation may include marked angioedema of the eyelids and involvement of the conjunctiva. Respiratory manifestations may include oral and pharyngeal swelling, hoarseness, laryngospasm, wheezing, cough, breathlessness, and/or chest tightness. Cardiovascular manifestations may include hypotension, which may produce loss of consciousness, and arrhythmias.

ETIOLOGY

Many food and condiment proteins have been reported to cause anaphylaxis.[2,3] The greatest number of anaphylactic reactions to foods have been reported after exposure to peanuts or other legumes, true nuts, fish, shellfish, milk, and eggs, especially in children.[4-7]

It should not be assumed that a reaction to one member of a food family necessarily incriminates any or all other members.[8,9] There may be more cross-reactivity between foods and plants that are seemingly unrelated (ragweed and melons, latex and banana) than there is between foods which seem to be in the same family (legumes, such as peanuts and peas). Latex sensitivity has been associated with multiple and varied food sensitivities (see section on latex hypersensitivity).

HISTORY

Obtaining a thorough history from patients who have experienced a life-threatening reaction that may have been caused by a food is crucial. The history may be unequivocal, as in the individual who eats a single food (such as peanut) and shortly thereafter develops anaphylaxis. It should be remembered that highly sensitive patients may experience anaphylaxis after inhalation exposure. However, in many patients with anaphylaxis, no food offender can be immediately identified. If anaphylaxis occurs repeatedly and food allergy is suspected, it may be possible to assemble a list of ingredients from foods ingested before these events, searching for common constituents.

Anaphylactic reactions to foods almost always occur immediately after the food is ingested.[3] Symptoms may then subside only to recur several hours later. In addition, a biphasic reaction may occur with or without treatment of the immediate reaction.

Delayed or late anaphylactic reactions to foods are exceedingly rare and may occur because of prior absorption from the stomach and delayed gastric emptying.

It is important in evaluating suspected food allergy to consider associated factors such as exercise after food ingestion (see section on exercise-induced anaphylaxis).[10] It has been hypothesized that alcohol consumption may increase the chance of a food producing symptoms, but this has not been proven.

PHYSICAL EXAMINATION

When an individual is seen for evaluation of a possible anaphylactic reaction to food, there are usually no physical findings unless the person is seen during the acute event. Because this is uncommon, it is very important to attempt to obtain any medical records that might contain a description of the acute event, especially if vital signs were obtained at that time.

DIAGNOSTIC TESTING

Presently, the most useful diagnostic tests for food hypersensitivity include tests for specific IgE antibodies to foods and food challenges. In vitro testing with RAST or ELISA for IgE to foods is the safest procedure that can be used in screening for food allergy, but its accuracy depends on the reliability of the in vitro testing, the ability to interpret the results, and availability of reliable

testing material. If skin prick tests are performed in this setting, the extract that is used may need to be diluted substantially. It is important to recognize that although many food allergens have been well characterized, standardized food extracts are not currently available. If skin testing is performed, it should be done by a physician experienced in the procedure in a setting with appropriate rescue equipment and medications. In some instances, fresh food must be used because appropriate allergens might be degraded in the manufacture of allergens.

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 may be necessary because identification of the food may be life saving.[6] Double- or single-blind placebo-controlled food challenges can be performed safely in individuals with a history of food-induced anaphylaxis.[3, 7] However, it may 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 minute amount of food allergen can precipitate anaphylaxis.[11]

Occasionally, food challenges have been done with very small amounts of a whole meal to determine if anaphylaxis was due to some component of the meal or another trigger. If the challenge is performed with individual foods, consideration should be given to challenging the patient first with the least likely cause of the reaction and progressively challenging the patient with more strongly suspected foods.

PATIENT EDUCATION

Education about avoidance and management of accidental ingestion of foods known to produce anaphylaxis 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.[12, 13]

Patients with food hypersensitivity should be taught to effectively read and interpret labels on foods and to inquire about ingredients in restaurant meals. There are educational materials available from dieticians, 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 constitutes a special hazard for some students 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. 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. There is not general agreement about whether patients who have had generalized urticaria after food ingestion need to carry epinephrine.

If epinephrine is prescribed for the patient, the patient must understand that it should be available at all times. This instruction may 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 in a school setting 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 may help to define the specific food causing the reaction. If the cause of the patient's reactions is known, this interaction can reestablish that the food responsible for these reactions was correctly identified and that the appropriate treatment response was initiated.

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X. Avian-based vaccines

SUMMARY STATEMENTS

- Adverse reactions to avian-based vaccines have been attributed to the egg protein in the vaccine, as well as to hydrolyzed gelatin, sorbitol, and neomycin in some of the vaccines.
- True anaphylactic reactions to vaccines are rare, including those vaccines with minute quantities of avian protein (measles, mumps, yellow fever, and influenza).
- A careful history should be taken to document the symptoms and severity of prior allergic reactions to egg protein, vaccines, and agents contained in vaccines (e.g., gelatin).
- With a history of exquisite sensitivity (anaphylaxis) to egg protein, the utility of vaccine skin testing to predict vaccine reactions remains controversial. However, it may be considered in this high-risk group, particularly if influenza or yellow fever vaccine are to be administered. If the vaccine skin test response is negative, the vaccine can be given.
- If a positive skin test response to a vaccine is obtained, a desensitization protocol can be used to administer the vaccine, although desensitization is not believed to be necessary by some experts. Adverse reactions have been reported during skin testing and desensitization. Therefore, these procedures should be performed by personnel trained to treat anaphylaxis.

Anaphylactic reactions to components of vaccines are rare. Often it is difficult to differentiate between a reaction to the vaccine and a coincidental reaction. Because minute quantities of egg proteins can be found in vaccines such as measles, mumps, yellow fever, and influenza, the administration of these vaccines in individuals highly allergic to eggs may be a concern. However, most immediate sensitivity reactions to MMR (measles, mumps, rubella) vaccine appear to be due to other vaccine components, such as gelatin or neomycin.

SKIN TESTING

Current measles and mumps vaccines are derived from chick embryo fibroblast tissue cultures and do not contain significant amounts of proteins that cross-react with eggs. The 1997 recommendation of the American Academy of Pediatrics Committee on Infectious Diseases suggests that children with egg allergy routinely may be given MMR, measles, or mumps vaccine without prior skin testing, although some experts recommend that such individuals be observed for 90 minutes with immediate availability of equipment for emergency medical treatment of anaphylaxis. Previously, it was suggested that if a positive skin test response to the vaccine and a history of severe egg sensitivity was present, a patient should be desensitized with the vaccine by using

the following schedule: (1) 0.05 ml 1:10 dilution, (2) 0.05 ml full strength, (3) 0.10 ml full strength, (4) 0.15 ml full strength, and (5) 0.20 ml full strength. Doses are given subcutaneously at 20-minute intervals. Because there are reports that avian-based vaccines can be given safely in most individuals allergic to eggs, routine desensitization may not be necessary in such patients.[1-15] Furthermore, despite a positive skin prick test response to MMR vaccine, patients have tolerated this vaccine with no adverse effect. Thus the specificity and sensitivity of skin testing with MMR to predict vaccine safety is questioned.[1]

Current yellow fever and influenza vaccines also contain egg proteins and, on rare occasions, may induce immediate allergic reactions, including anaphylaxis. Skin testing with yellow fever vaccines is recommended before administration to persons with a history of systemic anaphylactic symptoms (generalized urticaria, hypotension, and/or manifestations of upper or lower airway obstruction) after egg ingestion. Skin testing with influenza vaccine has been used also in children with a history of severe, anaphylactic reactions to eggs who are to receive this vaccine. However, these children generally should not receive influenza vaccine in view of the risk of reaction and the need for yearly vaccination. Less severe or localized manifestations of allergy or allergy to feathers are not contraindications to yellow fever or influenza vaccine administration and do not warrant vaccine skin testing.[16]

ADVERSE REACTIONS

Adverse reactions to avian-based vaccines have been reported in individuals allergic to egg protein.[9] One of the proposed mechanisms of action is the presence of specific IgE to a minute quantity of egg protein or other proteins in the vaccine that cross-react with egg protein. Anaphylactic reactions to measles vaccine have occurred in patients without a history of egg hypersensitivity.[10, 17-19] Such reactions have been attributed to other components, such as neomycin, hydrolyzed gelatin, sorbitol, or stabilizers. Recently, IgE to the gelatin component of the vaccine has been demonstrated, suggesting gelatin as the etiologic agent in some cases[10]; however, the cause remains unknown in many cases. Thus the possibility of an immediate adverse reaction to these vaccines remains, regardless of the patient's atopic history or history of egg sensitivity.[12]

Currently, the MMR vaccine is prepared in chick embryo fibroblast cell culture. This refined technique decreases the amount of protein that cross-reacts with egg ovalbumin to an amount believed unlikely to cause anaphylaxis.[20] The yellow fever vaccine and the influenza vaccine are prepared in embryonated eggs and contain a higher amount of egg protein than the MMR vaccine. Multiple studies support the safety of adminis-

tration of the MMR vaccine or individual components of this vaccine in egg-sensitive children.[1-3, 5-8, 11-15] A study of 140 egg-sensitive children showed that at least 97.5% of this patient population will tolerate the vaccine without significant difficulty.[1] In a total of 17 studies, MMR vaccine was safely administered in a single-dose fashion to 1209 patients with a positive skin test response to egg, indicating that at least 99.75% of children who are allergic to eggs and have a positive skin test response can receive this vaccine in the usual fashion without having a severe anaphylactic reaction. Only two (0.16%) of 1227 patients who were allergic to eggs and received the vaccine in the usual dose had any symptoms suggesting anaphylaxis. Persons with a history of egg allergy have tolerated the yellow fever vaccine as well.[13] Asthmatic children with a history of egg sensitivity and a positive skin test response to influenza vaccine were safely administered the influenza vaccine by using a desensitization procedure. However, it is unknown if these patients could have safely received the recommended dose without desensitization. Because the potential for reactions to vaccines are unpredictable, and immediate hypersensitivity reactions can occur, they should only be administered in a supervised setting.

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XI. Insect stings and bites

SUMMARY STATEMENTS

- Insects from the Hymenoptera order can cause systemic allergic reactions in sensitized patients.
- Reactions to insect stings may include local, as well as generalized, skin, respiratory, and/or vascular reactions. There are no data that large local reactions predispose patients to systemic reactions.
- Late reactions after insect stings include serum sickness–like syndromes, some of which are not IgE-mediated.
- Immediate hypersensitivity skin testing with venom to honeybee, wasp, yellow jacket, yellow hornet, and white-faced hornet venoms is the most sensitive method for determining specific IgE sensitivity in patients who have had anaphylactic reactions from stings of these insects.
- Skin tests with whole body extract from fire ants and *Triatoma* species should be used to document IgE sensitivity in patients with reactions to these types of insects.
- Immunotherapy with Hymenoptera venom for honeybee, yellow jacket, white-faced hornet, yellow hornet, and wasp venom is extremely efficacious and is recommended for patients with anaphylactic reactions after Hymenoptera stings.
- Immunotherapy with Hymenoptera venom is currently recommended for a period of 3 to 5 years, but the duration of venom immunotherapy should be individualized.
- The imported fire ants (IFAs) *Solenopsis invicta* and *Solenopsis richteri* are responsible for significant allergic reactions. The typical result of an IFA sting is the development of a pruritic wheal and flare at the site of the sting within 20 minutes. Six hours later, a pustule forms, which continues to develop for the next 24 hours.
- Systemic reactions to IFA stings exhibit a spectrum that is similar to those reactions after stings of other Hymenoptera species. From 2% to 4% of patients have been reported to have serious systemic anaphylactic reactions after IFA stings.
- The diagnosis of IFA sting reactions includes a history of a typical fire ant mound in the vicinity of the sting incident and the presence of a typical pustule at the sting site. Documentation of specific IgE sensitivity to IFA is usually performed by skin testing with imported fire ant whole body extract (IFA-WBE).
- IFA-WBE extracts are sensitive for determining specific IgE sensitivity in patients who have had a history of generalized systemic anaphylactic reactions. In vitro testing with whole body extract (WBE-RAST) is not as sensitive as skin testing for determining IFA sensitivity.

- *Triatoma*, indigenous to the southwest, is a nocturnal, blood-sucking arthropod whose bite can produce anaphylaxis. Skin testing can be used to confirm the diagnosis and subsequent reactions can be prevented by allergen immunotherapy. Other biting insects may occasionally cause anaphylaxis.

Stinging insects are members of the Hymenoptera order, which contains apids (honeybees, bumblebees, and sweatbees), vespids (yellow jackets, hornets, and wasps), and formicids (ants). The self-reported prevalence of insect sting allergy is approximately 0.5% to 1%. There are about 40 deaths annually from insect stings in the United States and about 20 in Europe.

Diagnosis and optimal management of stinging insect allergy depends on successful identification of the insect, accurate classification of the reaction, and knowledge of the natural history of stinging insect allergy.

INSECTS

The geographic distribution of stinging insects is variable. Yellow jackets, white- and yellow-faced hornets, wasps, and domestic honeybees are found throughout the United States, whereas fire ants and African honeybees are indigenous to the southern and southwestern regions. Domestic honeybees in the United States *(Apis mellifera)* are mild mannered and will not sting unless provoked; their barbed stinger with attached venom sac will remain embedded in the sting victim. African honeybees *(Apis mellifera* Scutellata) have more defensive and hostile behavior and will attack in swarms without provocation.[1] Yellow jackets are scavengers and are also aggressive. Imported fire ants (IFAs) anchor themselves by their mandibles and deliver multiple stings in a semicircular pattern. A sterile pustule usually forms at each sting site. Bumblebees and sweatbees infrequently cause sting-induced anaphylaxis.

CLASSIFICATION OF REACTIONS

Systemic allergic reactions to stings must be differentiated from local reactions (e.g., swelling of the area around the sting site in which the signs and symptoms are contiguous with the sting site), especially large local reactions, and from toxic reactions, which occur after multiple stings. In the latter case the signs and symptoms may be identical to anaphylaxis, but are produced by vasoactive compounds in the venom itself rather than by vasoactive materials released after allergen-IgE antibody reaction on mast cell surfaces. Delayed reactions (>4 hours after the sting) may include a serum sickness–like syndrome, Guillain-Barre syndrome, glomerulonephritis, or myocarditis. The pathophysiology of most delayed reactions is unclear. Diagnostic studies are not indicated in persons experiencing large local reactions

because there are no data that these reactions predispose patients to systemic reactions.

NATURAL HISTORY OF INSECT STING SENSITIVITY

In adults with a history of insect sting anaphylaxis who do not receive venom immunotherapy, the risk of stinging insect anaphylaxis with future stings ranges from 30% to 60%. Hypersensitivity can be lost spontaneously without treatment.[2] Children who have experienced only cutaneous angioedema and/or generalized urticaria after insect stings have only a 5% to 10% risk of systemic reactions with future stings.[3] In a European study, the risk of future sting anaphylaxis was estimated at 52% for untreated honeybee-sensitive persons but only 25% for untreated yellow jacket–sensitive individuals.[4] Sting-sensitive persons who do not receive venom immunotherapy should be instructed on insect avoidance and the proper use of epinephrine-containing emergency kits.

DIAGNOSIS

The diagnosis of stinging insect hypersensitivity requires a typical clinical history and demonstration of venom-specific IgE antibodies. Because intracutaneous skin tests are more sensitive than immunoassays for identifying venom-specific IgE, skin testing is the preferred diagnostic test. Lyophilized preparations of honeybee, wasp, yellow jacket, yellow hornet, and white-faced hornet venoms are available for use. Positive skin test responses at venom concentrations of 1 μg/ml or less are considered significant. Only whole body extracts are available for diagnosing fire ant or sweatbee hypersensitivity and they have proven to be diagnostically useful.

IMMUNOTHERAPY

Venom immunotherapy is medically indicated in adults who have experienced a systemic reaction to an insect sting and who have positive skin test responses to one or more insects. The decision to use or withhold venom immunotherapy in children with only cutaneous signs and/or symptoms after stings should be made on an individual basis.

Venom immunotherapy is generally well tolerated,[5] and a variety of immunization schedules have been published. At a maintenance dose of 100 μg, the efficacy of vespid venom immunotherapy is 98%; the efficacy of honeybee venom immunotherapy is a bit lower. Some experts recommend monitoring venom-specific IgG antibody levels during the first 2 or 3 years of venom immunotherapy, with upward adjustment of the venom maintenance dose if the IgG level is less than 3 μg/m, whereas others do not consider such testing worthwhile. Despite the ability of nearly all venom-treated patients to tolerate stings without systemic reactions, skin test responses of many patients do not revert to negative. Most patients can discontinue venom treatment after 3 to 5 years, irrespective of venom-specific IgE/IgG levels or skin test results, with the longer period of treatment advised

for persons who have experienced more severe sting reactions. Preliminary evidence suggests that in patients who discontinue venom immunotherapy after 3 to 5 years, the risk of insect sting anaphylaxis is approximately 8% to 14%.[6-10] It is to be noted that these data are derived from studies of Hymenoptera venom immunotherapy. Thus they may not apply to patients who receive whole body extract to treat IFA anaphylaxis.[11]

IFA HYPERSENSITIVITY

Physician surveys in areas endemic for IFAs indicate that approximately 7% of patients require treatment annually for reactions to IFA stings.[12] The IFAs *Solenopsis invicta* and *Solenopsis richteri* belong to the Hymenoptera order. Significant reactions can occur to IFA stings. The typical reaction consists of a painful sting site with a pruritic wheal and flare within 20 minutes. Six hours later, a pustule forms and becomes fully developed in about 24 hours. This pustular lesion is characteristic of IFA stings.[13] In addition, IFA stings can produce large local reactions that evolve into a second phase of pruritic erythema and induration and become more prominent 6 to 24 hours later. The typical local pustule is also present in this type of reaction. Systemic reactions from imported fire ant stings exhibit a spectrum that is similar to reactions after stings from other Hymenoptera species. The main differentiating characteristic is the pustule, which is found at the fire ant sting site. In physician surveys, 2% to 4% of patients have reported serious systemic anaphylactic reactions after IFA stings.[11, 14, 15] Seventeen to fifty-six percent of patients reportedly have large local reactions to IFA stings.[16]

The diagnosis of fire ant allergy is made on the basis of the presence of a characteristic pustule at the sting site and the presence of the typical fire ant mound in the vicinity of the sting incident. Imported fire ant whole body extract (IFA-WBE) is the only reagent presently available for diagnostic testing and immunotherapy for fire ant hypersensitivity. The *Solenopsis invicta* and *Solenopsis richteri* species cross-react, and clinically *Solenopsis invicta* extract is used exclusively. Documentation of specific IgE sensitivity to IFA stings is usually performed by skin testing with IFA-WBE. Skin testing with IFA-WBE is quite sensitive.[17] It has been reported that 78% of patients with allergic reactions to IFA are reactive to IFA-WBE.[18] RAST testing has not been as useful for detecting IFA IgE antibodies. Only 48% of patients with allergic reactions to IFA stings had positive responses to WBE-RAST.[19] Several studies have documented the clinical effectiveness of IFA-WBE immunotherapy for patients who have had systemic reactions after IFA stings.[14, 20, 21] IFA venom is present in whole body extracts.[22] Immunotherapy consists of weekly subcutaneous injection of IFA-WBE extract with increasing dosages to an empirically determined maintenance level, which is usually 0.5 ml of a 1:10 dilution of commercially

available IFA-WBE. In patients who discontinued IFA-WBE immunotherapy after 2 to 19 years, it was found that 76% still had positive skin test responses, but 94% had no reactions on re-sting.[23] Moreover, the retrospective analysis of patients with systemic allergic reactions to IFA stings who received immunotherapy have shown a low reaction rate on field stings.[24]

TRIATOMA

The reduvid bug *(Triatoma protracta* and *T rubida)* is a nocturnal, blood-sucking arthropod found in the southwestern United States. Bites occur at night and are painless. At these times, patients can become sensitized by salivary gland allergens. Because patients do not awaken from the bite, exposure and sensitization may not be recognized. Although the true incidence is unknown, serologic studies suggest that the prevalence of IgE-mediated sensitivity is about 6% in areas where these insects are found. Anaphylactic reactions after *Triatoma* bites have been reported and should be suspected whenever a patient in an area of exposure awakens at night with anaphylaxis. Skin testing has been used to confirm the diagnosis, and subsequent reactions have been effectively prevented by allergen immunotherapy.[24, 25]

HARVESTER ANTS

Harvester ants *(Pogomyrex maricopa* and *rugosus)* in the western and southern United States may be occasional causes of anaphylaxis. Harvester ants usually construct large nests in sand or soil fully exposed to the sun. They have large mandibles that enable them to carry seeds and destroy vegetation and a posterior stinging apparatus similar to IFAs. There is little cross-reactivity between allergens in harvester ant venom and those in IFAs or other Hymenoptera. Local reactions to harvester ants do not cause sterile pustules.[26]

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XII. Latex

SUMMARY STATEMENTS

- Latex (rubber) hypersensitivity is a significant medical problem, and three groups are at higher risk of reactions: health care workers, children with spina bifida and genitourinary abnormalities, and workers with occupational exposure to latex.
- To identify IgE-mediated sensitivity, 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. Although a standardized, commercial skin test reagent for latex is not yet available in the United States, many allergy centers have prepared latex extracts for clinical testing. In vitro assays for IgE to latex may also be useful, although these tests are generally less sensitive than skin tests.
- 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-controlled environment.
- A latex-controlled environment is defined as 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.
- 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 may minimize latex sensitization of health care workers and patients and should reduce the risk of inadvertent reactions to latex in previously sensitized individuals.
- Patients with a diagnosis of latex allergy by history or skin testing should wear a medical identification bracelet, carry a medical identification card, or both. If patients have a history of anaphylaxis to latex, it may be important for them to carry epinephrine and antihistamines for self-administration.

In the last several decades, a significant new medical problem has emerged throughout the world: latex (rubber) hypersensitivity. Even though latex products have been used for over a century, it appears that the increased use of these products to prevent contact with the HIV virus has led to the increased incidence of latex sensitivity.

Natural rubber is produced from coagulating sap (latex) from the common rubber tree *Hevea brasiliensis*. Latex is composed primarily of rubber hydrocarbons, with small amounts of protein, acetone residues, fatty acids, sugar, and mineral matter. The proteins in latex

sap are the source of an array of water-soluble allergens present in latex rubber articles.[1]

Latex rubber is used in thousands of products by both the general public and medical personnel. The major nonmedical rubber products include rubber gloves, shoes, condoms, balloons, underwear elastics, and belts. Medical personnel are exposed to a high number of rubber articles, with latex gloves being the most important. Other commonly used rubber products in medicine and dentistry include endotracheal tubes, adhesive tape, urinary catheters, stomach tubes, and cofferdams.[1-3]

Individuals can be exposed to latex by contact, parenteral administration, or aerosol transmission. Aerosol exposure from powdered latex gloves occurs primarily because of absorption of latex allergens to cornstarch powder that then becomes airborne. Mucosal contact and parenteral administration pose the greatest risk for anaphylaxis and can cause life-threatening reactions in patients with previously mild cutaneous or respiratory reactions.

Immediate allergic reactions to rubber were first reported in the late 1970s.[4] Contact hand dermatitis may precede development of generalized latex reactions, such as urticaria, angioedema, respiratory reactions, and cardiovascular collapse.[1,5,6] On the other hand, anaphylaxis may occur without previously recognized manifestations.[1]

It has become clear that three major groups are more likely to have systemic allergic reactions to latex: children with spina bifida or genitourinary abnormalities, health care workers, and other workers with occupational exposure to latex. Atopic patients are at increased risk for having latex sensitivity.[1,7-10]

Evidence of IgE-mediated sensitivity to foods (as assessed by skin prick testing or in vitro tests) is common in latex-sensitive patients (>50% of patients in some series). However, only a minority of patients allergic to latex have clinical reactions after food ingestion (27% of patients with positive skin test responses in one series).[11] Clinical and in vitro cross-reactivity (demonstrated by in vitro inhibition analyses) has been reported between latex and avocado, banana, chestnut, potato, tomato, and kiwi fruit.

Recognition of latex sensitivity and prevention of reactions in the latex-sensitive patient are of paramount importance. Both the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology have published recommendations for the evaluation and management of patients allergic to latex.[12,13]

Patients in high-risk groups (children with spina bifida and genitourinary abnormalities, health care workers, and patients with other occupational exposure to latex) should be queried about possible latex allergy, especially if surgery or a medical procedure is planned. Patients

who are members of these high-risk groups, those with a medical history suggestive of latex allergy, and patients with a positive test response for latex-specific IgE antibodies are at increased risk for anaphylaxis to latex.

Skin tests for the detection of latex immediate hypersensitivity should be considered in patients who are members of high-risk groups or who have a clinical history of possible latex allergy. Although a standardized, commercial skin test reagent for latex is not yet available in the United States, many allergy centers have prepared latex extracts for clinical testing. In vitro IgE assays for latex may also be useful, although these tests are generally less sensitive than skin tests.[14]

Medical and operative procedures in high-risk patients should be conducted in a latex-controlled environment. A latex-controlled environment is defined as an environment in which no latex gloves are used in the room or surgical suite and in which all direct contact with latex accessories (catheters, adhesives, tourniquets, and anesthesia equipment) has been eliminated. Nonlatex synthetic rubber articles that do not contain latex allergens, and should be substituted for latex articles whenever possible. The elimination of latex gloves in the operative suite is especially important. When possible, high-risk surgical patients should be scheduled as the first case of the day to reduce latex exposure.

The use of powder-free latex gloves has been shown to prevent significant airborne latex exposure and the development of respiratory reactions in sensitized individuals.[15, 16] Sensitive individuals still need to avoid direct contact with latex articles.

Latex gloves have been developed with negligible latex allergen content. 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 an approach may minimize latex sensitization of health care workers and patients and should reduce the risk of inadvertent reactions to latex in previously sensitized individuals.

Patients at increased risk of anaphylaxis to latex may benefit from carrying a medical identification bracelet or card.

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XIII. β-lactam antibiotics

SUMMARY STATEMENTS

- Penicillin is the most frequent cause of anaphylaxis in humans and has been estimated to be responsible for 75% of anaphylactic deaths in the United States.
- Although allergic reactions may occur after administration of penicillin by any route, parenteral administration is most likely to induce severe reactions such as anaphylaxis. Oral administration appears considerably safer.
- Patients with a history of a prior penicillin reaction are six times more likely to experience a reaction on subsequent exposure compared to those without a previous history.
- Over 80% of patients with a history of allergy to penicillin do not have penicillin-specific IgE antibodies as detected by skin testing.
- If a patient requires penicillin and has a past history of penicillin allergy, it is necessary to skin test the patient for the presence of penicillin-specific IgE antibodies before assuming that the patient will not be able to tolerate penicillin.
- Skin testing identifies patients with IgE antibodies specific for penicillin who, as a result, may be at risk of an immediate reaction if given penicillin.
- Skin testing for penicillin does not predict the later development of IgE-mediated reactions or reactions caused by other immune mechanisms.
- IgE antibodies to minor determinants are most frequently implicated in anaphylactic reactions to penicillin.
- Evaluation by RAST or ELISA testing does not reliably rule out allergy to penicillin because of the insensitivity of the test and the lack of an appropriate minor determinant reagent.
- Patients with a history of possible allergic reaction to penicillin who have a recommended indication for penicillin treatment should be skin tested.
- After anaphylaxis, there is an interval of time during which skin test results may not be reliable. This interval has been reported to vary from 1 to 2 weeks or longer.
- Skin testing is generally not recommended for a patient with a history of an exfoliative dermatitis, (Stevens-Johnson Syndrome, or toxic epidermal necrolysis) from penicillin or other β-lactam medications.
- Patients with a positive family history but no personal history of penicillin allergy do not require penicillin skin testing because they are generally not at risk of having an allergic reaction to penicillin.
- If skin test responses to penicillin with major (penicilloyl) and minor determinants (penicillin G and others) are negative, 97% to 99% of patients (depending on reagents used) will tolerate penicillin

administration without risk of an immediate reaction. By using the above reagents and proper technique by skilled personnel, serious reactions, including anaphylaxis and death, are extremely rare.
- If a patient has a positive history and a positive skin test response to penicillin, there is a 50% or greater chance of an immediate reaction if penicillin is given again.
- If the patient has a past history of an allergic reaction to penicillin and the skin test response is positive to either major or minor determinants, the patient should receive an alternative antibiotic unless the indication for penicillin is clear. If administration of penicillin is mandatory in this setting, desensitization is indicated.
- If the patient has a past history of allergy to penicillin and the skin test response is negative to penicilloyl polylysine and penicillin G, there is a small chance that specific IgE antibodies to other minor determinants not contained in penicillin G may be present.
- Administration of ampicillin and amoxicillin is associated with the development of morbilliform rashes in 5% to 13% of patients. These patients should not be considered at risk of a life-threatening reaction to penicillin and therefore do not require skin testing. On the other hand, if the rash to ampicillin or amoxicillin is urticarial, or if the patient has a history of anaphylaxis, the patient should undergo penicillin skin testing before a future course of penicillin is given.
- Carbapenems (e.g., imipenem) should be considered cross-reactive with penicillin. Aztreonam, a monobactam rarely cross-reacts with penicillin.
- Cephalosporins and penicillins have a common β-lactam ring structure, and varying degrees of cross-reactivity have been documented. However, the risk of allergic reactions to cephalosporins in patients allergic to penicillin appears to be low (less than 10%). First generation cephalosporins may pose a greater risk than second or third generation cephalosporins.
- If a patient has a questionable history of penicillin allergy and requires a cephalosporin, penicillin skin testing can be considered to ensure the absence of penicillin-specific IgE antibodies.
- If there is consideration of cephalosporin use in a patient who has a history of an immediate-type reaction to penicillin, skin testing to major and minor determinants of penicillin should be done to determine if the patient has penicillin-specific IgE antibodies. If the skin test response is negative, the patient can receive a cephalosporin at no greater risk than the general population.

- If there is consideration of cephalosporin use in a patient with a history of penicillin allergy who has a positive skin test response to penicillin, the physician's recommendations may include: (1) administration of an appropriate alternative antibiotic; (2) a cautious graded challenge (test dosing) with appropriate monitoring, recognizing that there is at least a 5% chance of inducing an anaphylactic reaction; or (3) desensitization to the cephalosporin that is proposed for use.
- Patients with a history of IgE-mediated reaction to a cephalosporin who require penicillin should undergo penicillin skin testing. If the test responses are negative, they can receive penicillin; if positive, they should either receive an alternative medication or undergo desensitization to penicillin.
- If a patient with a past history of allergy to one cephalosporin requires another cephalosporin, skin testing with the required cephalosporin can be done, recognizing that the negative predictive value is unknown. If the skin test response for the cephalosporins is positive, control subjects can be tested to determine if the positive response was caused by irritation or was IgE-mediated.

PENICILLIN
Epidemiology

Penicillin is the most frequent cause of anaphylaxis in humans[1] and has been estimated to be responsible for 75% of anaphylactic deaths in the United States.[2] Most deaths from penicillin anaphylaxis have occurred among individuals with no history of atopic disease.[3] Anaphylactic reactions to penicillin occur most commonly in adults between the ages of 20 and 49 years, although such reactions have occurred in both children and the elderly.[4] A fatal outcome, however, may be more likely in the older patient because of compromised cardiovascular status and the use of multiple medications, including the use of β-adrenergic blocking drugs.[4]

Although allergic reactions may occur after administration of penicillin by any route, parenteral administration is most likely to induce severe reactions such as anaphylaxis. Oral administration appears considerably safer.[5] Up to 20% of hospitalized patients claim to have a history of allergy to penicillin. Some of these histories may not be consistent with penicillin hypersensitivity. Nevertheless, many of these patients receive alternative antimicrobial drugs. Alternative antibiotics should not be chosen simply on the basis of a positive history without documentation by appropriate skin testing.[6, 7]

Definition of terms

β-lactam antibiotics are drugs that have a common β-lactam ring structure. This includes penicillins, cephalosporins, carbapenems (e.g., imipenem), and the monobactam, aztreonam. Graded challenge is a descriptive term for a test dosing procedure that can be used in patients with a history of an adverse/allergic reaction that is not consistent with an IgE-mediated mechanism.

The principle of a graded challenge protocol is based on the administration of small doses of the drug with incremental progression at regular intervals to full dose therapy. Desensitization is the rapid progressive administration of an allergenic substance to render effector cells less reactive.

EVALUATION OF PENICILLIN ALLERGY

Although the history alone is not diagnostic of penicillin hypersensitivity, it may be helpful in the initial assessment. Patients with a history of prior penicillin reaction are six times more likely to experience a reaction on subsequent exposure compared with those without a previous history.[8] Nevertheless, there are reasons why a previous history of penicillin hypersensitivity may not be reliable. For example, minor rashes in childhood may be misdiagnosed as penicillin allergy. In addition, a majority of patients with documented hypersensitivity to penicillin lose this hypersensitivity with time.

Over 80% of patients with a history of allergy to penicillin do not have penicillin-specific IgE antibodies as detected by skin testing.[9] However, if a patient requires penicillin and has a past history of penicillin allergy, it is necessary to skin test the patient for the presence of penicillin-specific IgE antibodies before assuming that the patient will not be able to tolerate penicillin.[8, 10-13] Skin testing identifies patients who have IgE antibodies specific for penicillin and, as a result, may be at risk of an immediate reaction if given penicillin. Skin testing for penicillin does not predict the later development of IgE-mediated reactions or reactions caused by other immune mechanisms.[14] IgE antibodies to the minor determinants are most frequently implicated in anaphylactic reactions to penicillin.[15] Testing for specific IgE antibodies to penicillin should be done shortly before the administration of penicillin and repeated before each subsequent course of β-lactam antibiotic therapy among patients with a history of a previous IgE-mediated reaction to penicillin.[16] This type of testing determines whether specific IgE antibodies to penicillin are present at the time of application. Evaluation by RAST or ELISA testing is not reliable to rule out allergy to penicillin because of the insensitivity of the test and the lack of an appropriate minor determinant reagent.

SELECTION OF PATIENTS FOR PENICILLIN SKIN TESTING

Patients with a history of a possible allergic reaction to penicillin who have recommended indications for penicillin treatment should be skin tested. This includes patients with a history of anaphylaxis, urticaria, or other rashes, as well as patients with unknown childhood or adult reactions. Individuals who have experienced anaphylaxis to penicillin cannot be reliably skin tested for 1 to 2 weeks or longer after the reaction.[17-19] Skin testing is generally not recommended for a patient with a history of an exfoliative dermatitis, Stevens-Johnson

syndrome, or toxic epidermal necrolysis from penicillin or other β-lactam medications.

Patients with a positive family history but no personal history of penicillin allergy do not require penicillin skin testing because they are generally not at risk of having an allergic reaction to penicillin. Interpretation of skin tests may be inaccurate if the patient is currently taking an antihistamine or another medication with antihistaminic properties. If skin testing for penicillin using major and minor determinants is negative, 97% to 99% of patients (depending on the reagents used) will tolerate penicillin administration without risk of an immediate reaction. If benzyl penicilloyl (the major determinant) and a mixture of minor determinants are used for skin testing, 99% of patients who have negative skin test responses will tolerate penicillin. If, on the other hand, benzyl penicilloyl and penicillin G are used for skin testing, without other minor determinants, 97% or more of patients who have negative skin test responses will tolerate penicillin.[8] However, some patients who are at risk for anaphylactic reactions will be missed. Conversely, if a patient has a positive history and a positive skin test response to penicillin, there is a 50% or greater chance of an immediate reaction if penicillin is given again.

RISKS OF ANAPHYLAXIS FROM SKIN TESTING

By using the above reagents and proper technique by skilled personnel, serious reactions, including anaphylaxis and death, are extremely rare. Nevertheless, anaphylactic reactions and deaths from penicillin skin testing have been reported. However, these were all caused by administration of higher than recommended doses or intracutaneous testing not preceded by prick/puncture testing. Use of penicillin skin test reagents does not appear to resensitize the patient.

TREATMENT ON THE BASIS OF SKIN TEST RESULTS

If the patient has a past history of an allergic reaction to penicillin and the skin test response is positive to either major or minor determinants, the patient should receive an alternate antibiotic unless the indication for penicillin is clear. If administration of penicillin is mandatory in this setting, desensitization is indicated.

Although the patient does not need to undergo test dosing before receiving a full therapeutic dose. If skin test responses to a mix of minor determinants (if available) in addition to the major determinant are negative, a test dose may be considered as a conservative measure. If the patient has a past history of allergy to penicillin and his or her skin test response is negative to penicilloyl polylysine and penicillin G, there is a small chance that specific IgE to other minor determinants not contained in penicillin G may be present. In light of the slight possibility that these are present, the patient should receive a small test dose.

SPECIAL PROBLEMS

Administration of ampicillin and amoxicillin is associated with the development of morbilliform rashes in 5% to 13% of patients. These patients should not be considered at risk of a life-threatening reaction to penicillin and therefore do not require skin testing. On the other hand, if the rash to ampicillin or amoxicillin is urticarial, or if the patient has a history of anaphylaxis, the patient should undergo penicillin skin testing before a future course of penicillin is given.

Carbapenems (e.g., imipenem) should be considered cross-reactive with penicillin. Aztreonam, a monobactam, rarely cross-reacts with penicillin. Patients allergic to β-lactam antibiotics other than penicillin may have antibodies directed to side-chain structures rather than to the β-lactam ring. Such antibodies have the potential to cause anaphylaxis.

CEPHALOSPORIN ALLERGY

Cephalosporins and penicillins have a common β-lactam ring structure, and varying degrees of cross-reactivity have been documented. However, the risk of allergic reactions to cephalosporins in patients allergic to penicillin appears to be low (less than 10%). First generation cephalosporins may pose a greater risk than second or third generation cephalosporins. Some anaphylactic reactions to cephalosporins may be due to antibodies directed against specific side chains in these molecules rather than the β-lactam ring.

ADMINISTRATION OF CEPHALOSPORINS TO PATIENTS WITH A HISTORY OF ALLERGY TO PENICILLIN

If a patient has a questionable history of penicillin allergy and requires a cephalosporin, penicillin skin testing can be considered to ensure the absence of penicillin-specific IgE antibodies. If a patient has a history of an immediate systemic reaction to penicillin, skin testing to major and minor determinants of penicillin should be done to determine if the patient has penicillin-specific IgE antibodies. If skin test responses are negative, the patient can receive the cephalosporin at no greater risk than the general population.

In a patient with a history of penicillin allergy and with a positive skin test to penicillin, in whom there is consideration of cephalosporin use, the physician's recommendation may include any of the following: (1) administration of an appropriate alternative antimicrobial; (2) a cautious graded challenge (test dosing) with appropriate monitoring, recognizing that there is at least a 5% chance of inducing an anaphylactic reaction; or (3) desensitization to the cephalosporin that is proposed for use.[18]

ADMINISTRATION OF PENICILLIN TO A PATIENT WITH A HISTORY OF ALLERGY TO A CEPHALOSPORIN

Patients with a history of IgE-mediated reactions to a cephalosporin who require penicillin should undergo

penicillin skin testing. If the test responses are negative, they can receive penicillin; if positive, they should either receive an alternative medication or undergo desensitization to penicillin.

ADMINISTRATION OF A CEPHALOSPORIN TO A PATIENT WITH A PAST HISTORY OF ALLERGY TO A CEPHALOSPORIN

If a patient with a past history of allergy to one cephalosporin requires treatment with another cephalosporin, skin testing with the required cephalosporin can be done, recognizing that the negative predictive value is unknown. If the skin test response for the cephalosporin is positive, control subjects can be tested to determine if the positive response was due to irritation or was possibly IgE-mediated. Skin testing should be done with a prick/puncture technique and possibly be followed by intradermal testing with positive and negative controls. If the skin test response is positive, it implies the presence of drug-specific IgE antibodies, and the patient should either receive an alternative medication or undergo desensitization. If prick/puncture and intradermal test responses are negative, it is reassuring that the patient does not have specific IgE antibodies to cephalosporin. However, cephalosporin skin testing is not standardized, and the negative predictive value is unknown.

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XIV. ASA/NSAIDs

SUMMARY STATEMENTS

- Aspirin (ASA) and nonsteroidal antiinflammatory drugs (NSAIDs) are associated with a variety of non-IgE-mediated adverse effects. These include systemic reactions, such as rhinoconjunctivitis, bronchospasm, urticaria, angioedema, and laryngeal edema.
- There is no definitive skin or in vitro test to identify patients who are intolerant to ASA or NSAIDs. On the other hand, carefully performed oral ASA/NSAID challenges can be useful in making a more definitive diagnosis.
- Once a diagnosis has been made, avoidance is essential in preventing life-threatening reactions to these agents. This requires educating the patient about combination products (including over-the-counter medications) containing ASA or NSAIDs.
- Allergy/immunology specialists are frequently asked to clarify the risk of reactions to ASA/ NSAIDs and to devise a strategy for dealing with these therapeutic dilemmas.
- It may be useful to refer a patient suspected of being intolerant to ASA or a NSAID to an allergist-immunologist and/or center where oral ASA/ NSAID challenges are performed routinely in a well-equipped medical facility because of the possibility of life-threatening reactions that can occur from such challenges.
- If the ASA/NSAID challenge is positive, pharmacologic desensitization and continued treatment with ASA or NSAIDs can be used if there is a medical indication for this type of medication.

Aspirin (ASA) and nonsteroidal antiinflammatory drugs (NSAIDs) are associated with a variety of adverse effects,[1-3] which include systemic reactions, such as rhinoconjunctivitis, bronchospasm, urticaria-angioedema, and laryngeal edema.[4-6] Asthmatic patients who have coexisting nasal polyps or sinusitis may be at greater risk of such reactions.[7, 8] The potency of in vivo cyclooxygenase activity by NSAIDs correlates with their potency for precipitating reactions in ASA-sensitive patients. Agents that are less potent inhibitors of cyclooxygenase (e.g., acetominophen, sodium salicylate, and salsalate) are generally tolerated by ASA-sensitive patients.[9] There is no convincing evidence that ASA-induced reactions are IgE mediated.[10]

There is no reliable in vitro test that can identify patients who are sensitive to ASA or NSAIDs. Carefully performed oral ASA/NSAID challenges can be used, however, to make a more definitive diagnosis.[11, 12] Because ASA and NSAIDs may be important in managing diseases such as arthritis and preventing thromboembolic phenomena, establishing a diagnosis may be ex-

tremely important in the overall management of selected patients.

Avoidance of ASA/NSAIDs is critical in preventing life-threatening reactions in patients who have experienced systemic reactions to these medications. Because ASA in particular may be an inconspicuous component of combination drug products (including over-the-counter medications), substantial diligence on the part of the patient and the physician may be required.

Severe bronchospastic reactions to ASA and NSAIDs are not easily reversed by inhaled β-agonists. In many cases parenteral epinephrine may be required, and in some instances intubation and ventilation may be necessary.

Allergy specialists are asked frequently to clarify the risk of reactions to ASA/NSAIDs and to devise a strategy for dealing with these therapeutic dilemmas. Referral of the patient to an allergist-immunologist and/or a center where oral aspirin challenges are performed routinely in a well-equipped medical facility may be necessary because of the potential life-threatening reactions that can occur from such challenge. If the challenge result with a particular ASA/NSAID is negative, this does not rule out subsequent reactions to such medications. If the ASA/NSAID challenge result is positive, pharmacologic desensitization and continued treatment with ASA or NSAIDs can be utilized if there is a medical indication for this type of medication.

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XV. Anaphylactoid reactions to radiographic contrast material

SUMMARY STATEMENTS

- Anaphylactoid reactions to radiocontrast material (RCM) can occur after intravascular administration and during hysterosalpingograms, myelograms, and retrograde pyelograms.
- Anaphylactoid reactions to RCM are clinically indistinguishable from IgE-mediated immediate hypersensitivity anaphylactic reactions, although they do not appear to be associated with IgE or any other type of immunologic reaction.
- The treatment of anaphylactoid reactions to RCM is not different than the treatment of anaphylactic reactions caused by allergen-IgE interaction and resultant mast cell mediator release.
- Patients who have experienced previous anaphylactoid reactions from the administration of RCM are at risk for a repeat reaction. Estimates of this risk range from 16% to 44% for procedures with high osmolality RCM. Therefore the physician should consider other alternatives in managing such patients rather than procedures that require readministration of RCM.
- With pretreatment and the use of lower osmolar RCM, the risk of repeat anaphylactoid reactions is reduced to approximately 1%.
- Pretreatment regimens for prevention of repeat anaphylactoid reactions have consisted of oral glucocorticosteroids, H1 and H2 antihistamines, and other medications such as ephedrine.

Radiographic contrast material (RCM) is used in over 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.[1] Among the 5% to 8% of patients who experience an adverse reaction to conventional RCM, most have minor reactions that require no specific treatment.[2] 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.[3] With the recent development of lower osmolality RCM, it appears that the overall risk of anaphylactoid reactions is decreased to about ⅕ that of conventional RCM.[4]

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%.[5,6] Other patients at increased risk are asthmatic and atopic patients, as well as those receiving β-adrenergic blocking agents or ACE inhibitors and patients with cardiovascular disease.[7-9] Anaphylactoid reactions have occurred when RCM is used for hysterosalpingograms, myelograms, and retrograde pyelograms.[5] With pretreatment and the use of lower osmolar agents, the risk can be reduced to approximately 1%.[10]

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.[8]

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, H1 and H2 antihistamines, and other medications such as ephedrine. A regimen that has been commonly recommended in the past has been 50 mg prednisone given orally 13, 7, and 1 hour before administration of RCM; 50 mg diphenhydramine given orally or intramuscularly 1 hour before the administration of RCM; and 25 mg 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 H1 antihistamines, additional use of H2 antihistamines, and/or exclusion of ephedrine. If the patient has to undergo an emergency radiographic procedure, an emergency pretreatment protocol that has been used successfully consists of 200 mg hydrocortisone given intravenously immediately and every 4 hours until the RCM is administered, and 50 mg diphenhydramine given intramuscularly 1 hour before the administration of RCM.[9]

In a setting where RCM is being administered, a differential diagnosis may include adult respiratory distress syndrome or noncardiogenic pulmonary edema. In at least two reports of failure of standard pretreatment regimens to prevent anaphylactoid reactions, the initial reactions were apparently due to noncardiogenic pulmonary edema rather than anaphylactoid reactions.[11,12] 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 and ACE inhibitors may require more intensive and prolonged treatment. Therefore a careful benefit/risk assessment should be made in patients receiving β-adrenergic blocking agents and ACE inhibitors if there is a preexisting 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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XVI. Insulin anaphylaxis

SUMMARY STATEMENTS

- In general, the degree of insulin immunogenicity is in the following order: bovine is greater than porcine, which is greater than human. Although anaphylactic reactions to human insulin produced by recombinant DNA technology are rare, they can occur.
- Insulin-induced anaphylaxis is characterized by the same manifestations as anaphylaxis from other causes.
- Patients are more likely to experience anaphylaxis from insulin administration if therapy is interrupted.
- Skin testing with insulin can aid in making the diagnosis of insulin-induced anaphylaxis. In addition, skin testing can be used to select the least allergenic insulin for administration to patients who have a history of immediate hypersensitivity reactions to insulin, yet require insulin.
- Patients with a history of anaphylaxis to insulin can be desensitized to insulin if no alternative medications exist to treat their disease.

Anaphylaxis to insulin has been relatively uncommon since the introduction of human insulin produced by recombinant DNA technology; however, allergic reactions still occur.[1] The manifestations are the same as would be seen in patients who have anaphylaxis from other causes.

The insulin molecule is composed of two polypeptide chains that are linked by two disulfide bonds. The acidic A chain consists of 21 amino acids while the basic B chain is a 30 amino acid entity. There is species variation in amino acid sequence; bovine insulin, which is becoming relatively unavailable, differs from human insulin by three amino acids, whereas porcine insulin differs by only one amino acid. Exogenously produced human insulin is identical to endogenous human insulin in amino acid sequence. In general, the most immunogenic insulin is therefore bovine insulin, and the least immunogenic is human insulin, but this is not true for every patient.

Before 1972, commercial preparations of insulin contained up to 1000 ppm of impurities, which could be a source of immunogenicity.[2] Currently, extensive chromatographic processing of animal insulins is routine and "purified" insulins contain less than 10 ppm of impurities[3] and as a result are reported to be less immunogenic.[4]

Because human insulin can also be immunogenic, it is most likely that this results from alteration of the tertiary configuration of the molecule. Patients have been reported with IgE and IgG antibodies directed against each of the three commercially available insulins: bovine, porcine, and human.[5, 6] In two cases, patients were

at least as reactive to human insulin as they were to porcine insulin.

Most patients who receive commercially available insulin will develop antibodies to the insulin administered.[7] Positive skin test responses to insulin are reported in approximately 40% of patients receiving animal insulin despite lack of any history of clinically significant allergic reactions to insulin.[2]

Systemic allergic reactions to insulin generally occur when insulin therapy has been interrupted. When insulin is readministered, the patient has increasingly large local reactions at the site of injection and, eventually, anaphylaxis. If insulin therapy is definitely indicated, insulin should not be discontinued after anaphylaxis, but the subsequent dose should be reduced by ⅓ to ⅒ of the previous dose, depending on the severity of the anaphylactic reaction. Subsequent doses should be slowly increased by 2 to 5 units until a satisfactory therapeutic result is achieved. Because there is a small risk of anaphylaxis with each increase in dosage, a physician should be in attendance when injections are given until a therapeutic dose is achieved.

Desensitization may be cautiously attempted in a patient who has had anaphylaxis in the past to insulin when reintroduction of insulin therapy is definitely indicated.[8] Skin testing may be of value in selecting the least allergenic insulin for desensitization. If no emergency exists, desensitization can be done slowly over several days. If large local reactions or systemic reactions occur, the schedule for administration of increasing doses of insulin may need to be modified. In addition to anaphylaxis, hypoglycemia may occur from the frequent insulin doses required for desensitization. If an emergent condition such as diabetic ketoacidosis exists, rapid desensitization may be required.[8] The same dosage schedule may be used, and the doses can be given at 10 to 30 minute intervals subcutaneously or intravenously. After successful desensitization to insulin, patients generally have lower IgE antibody levels directed against insulin in their serum and lower cutaneous reactivity.[9] Over the ensuing weeks of therapy, most patients also have antibodies against other insulin epitopes. It is possible that this may also afford some protection against anaphylaxis.[10] In patients who have required desensitization, it is advisable to maintain the patient on therapy to obviate the need for future desensitization, with its attendant risks.

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XVII. Protamine

SUMMARY STATEMENTS

- Intravenous administration of protamine, a polycationic protein used to reverse heparin anticoagulation, may cause anaphylaxis, as well as transient elevations in pulmonary artery pressure and/or cardiovascular collapse.
- The pathogenesis of these acute reactions has not been proven, but both nonimmune and immune (IgE) mechanisms have been reported.
- Patients who previously required protamine-containing insulin or intravenous protamine are at significantly increased risk for having anaphylaxis and other adverse reactions from intravenous protamine.
- Although intracutaneous tests with protamine may be helpful in identifying a possible IgE-mediated response in selected cases, these tests must be interpreted with caution because they do not necessarily predict clinical sensitivity and do not identify all patients at risk.
- A variety of alternative approaches may be considered to avoid the need for protamine reversal of heparinization. Several alternative agents may be used for heparin reversal, but these are not readily available on an emergency basis. For patients at high risk for protamine reactions, one should attempt to obtain one of the alternative reversal agents prior to the procedure that requires heparin anticoagulation.
- Although premedication with antihistamines and corticosteroids may be considered in an effort to reduce protamine reactions, there are no controlled trials that have demonstrated that premedication is effective in this setting.

Protamines are polycationic proteins (4500 daltons) purified commercially from the sperm or matured testes of salmon or related fish. They are administered intravenously to reverse heparin anticoagulation and are added to insulin preparations (in neutral protamine Hagedorn [NPH] and protamine-zinc insulins) to delay insulin absorption and thereby prolong their pharmacologic effect.

Intravenous administration of protamine can cause acute reactions that may include anaphylaxis, urticaria, bronchospasm, hypotension, transient elevations in pulmonary artery pressure, cardiovascular collapse, and death.[1-4] These adverse reactions are thought to be caused by multiple putative mechanisms, including IgE-mediated reactions[5]; activation of complement[6]; direct, nonimmunologic histamine release from mast cells; inhibition of serum carboxypeptidase; potentiation of IgE-mediated histamine release[7]; and elevation in thromboxane B_2 and 6-keto-$PGF_{1\alpha}$ levels, causing pulmonary artery pressure elevation.[8,9] Although the reported incidence of intravenous protamine reactions varies, diabetic patients with a history of use of protamine-containing insulins have a 40- to 50-fold increased risk of reactions to intravenous protamine, occurring in 2.9% to 26.6% of these patients, versus 0.076% to 1.2% of the general population.[1,3,4,10] Although studies of reactions to intravenous protamine have suggested that in some circumstances specific IgE antibodies to protamine may be present only as an epiphenomenon and not causally related to the development of reactions, there is convincing evidence that specific IgE antibodies to protamine play a role in the pathogenesis of some reactions to intravenous protamine.[11]

Subcutaneous administration of NPH insulin has been reported to cause anaphylaxis induced by specific IgE antibodies directed to the protamine component in these preparations, although most immediate-type reactions to protamine-containing insulin preparations are apparently caused by specific IgE antibodies to insulin determinants.[12]

RISK GROUPS

Patients with a history of protamine-containing insulin use or intravenous protamine use[1] are at significantly increased risk for having anaphylaxis and other adverse reactions from intravenous protamine. Fish allergy has been speculated to be a possible risk factor in case reports of protamine sensitivity,[13,14] but there is no convincing evidence for this, and there is in vitro evidence for a lack of immunologic cross-reactivity between commercially available salmon extracts (derived predominantly from salmon muscle tissue) and protamine.[15] Vasectomized men have been shown to have IgE and other antibodies to protamine and similar human proteins, presumably because of immunologic responses to systemic absorption of sperm that occurs after vasectomy. Such men are probably at increased risk for protamine reactions.[16-18]

IDENTIFYING RISK

Because anaphylaxis to intravenous protamine apparently may occur by a variety of nonantibody-mediated mechanisms, immunologic testing to detect elevated levels of IgE or IgG antibodies to protamine (available from several immunologic reference labs) does not identify all patients at risk for having anaphylaxis caused by protamine. However, patients who have detectable IgE or IgG antibodies to protamine are at significantly increased risk for having anaphylaxis and other immediate-type reactions, as are patients with a prior history of protamine reactions, regardless of immunologic status.

Patients who have a history of protamine-containing insulin use are at increased risk for reactions to intravenous protamine even if they have no detectable levels of antibodies to protamine, although in one series, patients

who also had IgE antibodies to protamine were at highest risk for reactions, and all of their reactions were moderate to severe.[5] The presence of IgG antibodies to protamine was a significant, though less important, risk factor.

Intracutaneous skin testing with protamine at concentrations greater than 10 μg/ml have been reported to cause nonspecific skin responses. Intracutaneous skin testing with protamine at concentrations 10 μg/ml or less may identify some patients who have elevated serum levels of IgE antibodies to protamine and are at increased risk for anaphylaxis from protamine administration, but neither prick nor intracutaneous skin testing is a reliable test for identifying such patients.[1, 11] It has been reported that patients may have reactions to intravenous protamine and elevated levels of serum IgE antibodies to protamine detectable by in vitro antibody tests (RAST, ELISA), yet have negative skin tests to protamine and equivocal in vitro basophil histamine release induced by protamine.[11] One suggested explanation for this discrepancy is that protamine may be an incomplete or univalent antigen and must first interact with a tissue macromolecule to become a complete or multivalent antigen capable of eliciting IgE-dependent mediator release.[11]

It has been proposed that protamineinsulin might be a better skin test antigen than protamine because the protamine-insulin complex might serve as a multivalent antigen.[12] Although intracutaneous skin testing with NPH insulin at concentrations as high as 1 U/ml (containing 3 to 5 μg/ml protamine) does not cause nonspecific irritant responses, it is unknown whether skin testing with protamine insulin is superior or comparable to skin testing with protamine alone in identification of patients with IgE antibodies to protamine.[12] A positive skin test response to protamine-containing insulin could indicate either elevated levels of IgE antibodies to protamine, the protamine-modified insulin, or insulin itself. However, intracutaneous tests may not correlate with clinical sensitivity.

ALTERNATIVES TO PROTAMINE

Alternative approaches to protamine use should be considered when heparinization reversal is required in diabetic patients with a history of protamine-containing insulin use, as well as in other patients at increased risk for reactions from protamine. Some suggested alternative approaches include autoreversal of lower dose heparinization, use of heparin-bound heart bypass pump circuits (to avoid need for protamine reversal), chemical reversal of heparinization with hexadimethrine, or use of heparinase or platelet factor 4.[19-21] Platelet factor 4 and heparinase currently are investigational agents and are difficult to obtain. Hexadimethrine (Polybrene) is a quartenary ammonium polycationic salt that had formerly been used for reversal of heparinization after completion of cardiac surgery. However, hexadimethrine has since been replaced by protamine for this indication, chiefly because of its potential nephrotoxic-

ity. If sufficient time is available for preplanned use of this agent, information can be obtained by contacting the FDA Division of Gastrointestinal and Coagulation Drug Products, Rockville, MD 20857 (Phone: 301-443-0487).

MEDICATION PRETREATMENT

In the event that it is not possible to institute one or more of the above alternatives, consideration might be given to prophylaxis with antihistamines and corticosteroids before protamine administration, as is customary to prevent anaphylactoid reactions to radiographic contrast media. However, there are no controlled, prospective studies that demonstrate that this approach is reliable. There is concern, therefore, that premedication would fail to prevent IgE-mediated anaphylaxis from protamine, considering that medication pretreatment has failed to reliably reduce the risk of IgE-mediated reactions from other agents such as chymopapain and penicillin.[22-24]

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XVIII. Local anesthetics

SUMMARY STATEMENTS

- Anaphylactic reactions to local anesthetics or constituents of local anesthetics have been reported, although IgE-mediated systemic anaphylaxis to these agents is rare.
- Local anesthetics are classified into groups, including esters (aminobenzoate and benzoic acid subtypes), amides, ethers, and ketones.
- Provocative (graded) dose challenge should be considered when the cause of a reaction is unknown or proof of safety is required before administration.
- Reactions to additives such as parabens or sulfites may occur but are rare, and routine testing with these substances is not recommended.
- In patients who have had reactions to an ester-type local anesthetic, an amide should be considered for provocative (graded) dose testing. If the patient had a reaction to an amide, another amide might be considered because cross-reactivity among amides has not been documented.

Clinical manifestations of anaphylaxis have been reported after the use of local anesthetics. However, several reports suggest that the great majority of patients with a history of anaphylaxis to local anesthetics fail to demonstrate similar reactions on a provocative (graded) dose challenge.[1-5] Consistent with these findings, anaphylactic/anaphylactoid reactions to local anesthetics or to other constituents of local anesthetic preparations are rare.

CLINICAL PRESENTATION OF REACTIONS OCCURRING IN ASSOCIATION WITH LOCAL ANESTHETIC ADMINISTRATION

Excessive dosage, rapid absorption, or inadvertent intravascular injection of local anesthetic preparations can result in cardiovascular or neurologic symptoms. Preparations that contain epinephrine may be associated with side effects related to the inotropic, chronotropic, and vasoconstrictive properties of epinephrine. These effects may be potentiated in patients receiving monoamine oxidase inhibitors, tricyclic antidepressants, or β-adrenergic blocking agents.[6] Central nervous system reactions to local anesthetics may be excitatory (low level toxicity) or depressant (high level toxicity) in nature. Cardiovascular toxicity includes bradycardia, atrial fibrillation,[7] hypotension, and cardiovascular collapse.

Vasovagal (neurocardiogenic) syncopal reactions are not uncommon in the setting of dental procedures. Characteristically, hypotension from vasovagal syncope is accompanied by bradycardia, sweating, and pallor. Symptoms such as tightness in the throat and dyspnea are also common.

ETIOLOGIC CONSIDERATIONS

Local anesthetics may be classified into groups, including esters (aminobenzoate and benzoic acid subtypes), amides, ethers, and ketones. Contact dermatitis is the most common allergic reaction to local anesthetics. Patch test results in patients with contact dermatitis show cross-reactivity among amide local anesthetics.[8] However, there is limited evidence that local anesthetics produce IgE-mediated responses[9] and uncertain evidence for cross-reactivity in the production of IgE-mediated responses.

Multidose vials of local anesthetics sold in the United States contain 1 mg/ml of methylparaben as a preservative. Some epinephrine-containing local anesthetics contain 0.5 mg/ml of metabisulfite as a preservative. Sodium bisulfite is found in some preparations for spinal anesthesia. A few reports suggest that parabens and sulfites may induce the production of IgE antibodies,[10-12] but in vitro or in vivo testing for sensitivity to parabens or sulfites is not a standardized procedure. Reactions to parabens and sulfites in local anesthetics are very rare, and routine testing with these substances is not recommended. When confronted with the possibility that a patient may react to these preservatives, the pragmatic approach is to simply avoid preparations containing them. In addition, it is important to remember that patients may be exposed to other causes of anaphylaxis in settings where local anesthetics are administered (e.g., latex).

PROVOCATIVE (GRADED) DOSE TESTING WITH EPINEPHRINE-, SULFITE-, AND PARABEN-FREE LOCAL ANESTHETICS

Two large studies have demonstrated that carefully performed provocative dose challenges with selected local anesthetics are useful in the management of patients with a history of previous reaction.[2,3] Patients are skin tested with increasing concentrations of local anesthetics after an initial skin test with phosphate-buffered saline, which serves as a placebo control. False-positive (wheal and flare) reactions occur to intracutaneous tests with undiluted local anesthetics, such as 1% procaine; however, 1:100 dilutions do not cause such reactions.[2] A full-strength subcutaneous challenge is performed at the end of the skin testing if the skin test results are negative.

AN APPROACH TO PATIENTS WITH A HISTORY OF REACTIONS TO LOCAL ANESTHETICS

1. A detailed history should be obtained.
2. If the local anesthetic suspected of causing the reaction is known, then a local anesthetic from another class should be considered for administration. For instance, if the drug is an ester, an amide should be considered. If the drug is an amide, either an ester may be used or another amide probably can be used

because substantial cross-reactivity among amides has not been noted.

3. Provocative (graded) dose challenge is a reasonable choice when the drug causing the reaction is unknown or proof of safety is required before clinical use. Even if the history is not strongly suggestive of an anaphylactic/anaphylactoid reaction, provocative (graded) dose challenge can be helpful to reassure the referring practitioner and the patient that there is no increased risk of reaction. However, if no procedure requiring an anesthetic is to be immediately performed, testing may be deferred.

4. A preparation without epinephrine, and ideally without parabens or sulfites, should be used for testing and treatment. These preparations are available through hospital pharmacies or wholesale drug distributors.

5. Skin testing and challenge should be undertaken only by individuals with training and experience in performing such tests and in the treatment of anaphylactic reactions.

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

SUMMARY STATEMENTS

- The incidence of generalized anaphylactic reactions during anesthesia have 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.
- It may be difficult to differentiate between immune and nonimmune mast cell–mediated reactions and pharmacologic effects from the variety of medications administered during general anesthesia.
- Thiopental allergy has been documented by skin tests.
- Neuromuscular blocking agents such as succinylcholine can cause nonimmunologic histamine release, but there have been reports of IgE-mediated mechanisms in some cases.
- Reactions to opioid analgesics are usually caused by direct mast cell–mediator release rather than IgE-dependent mechanisms.
- Antibiotics that are administered perioperatively can cause immunologic or nonimmunologic generalized reactions.
- Protamine can also cause severe reactions through IgE-mediated or nonimmunologic mechanisms.
- Latex is a potent allergen, and IgE-mediated reactions to latex during anesthesia have been clearly documented. Patients with multiple surgical procedures (e.g., 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.
- Ethylene oxide anaphylactic reactions have been reported particularly in patients who have exposure to hemodialysis or who are undergoing plasmapheresis.
- Blood transfusions can elicit a variety of systemic reactions, some of which may be IgE-mediated or mediated through other immunologic mechanisms.
- Methylmethacrylate (bone cement) has been associated with hypotension and various systemic reactions, although no allergic mechanism has yet been documented.
- The evaluation of allergic reactions to medications used during anesthesia can include skin testing to a variety of anesthetic agents.
- The management of anaphylactic reactions that occur during general anesthesia is similar to the management of anaphylaxis in other situations.

INCIDENCE

Determining the incidence of anaphylactic reactions during anesthesia or the intraoperative and postoperative periods is difficult because they are often attributed to toxic, pharmacologic, or anesthetic effects rather than allergy. Urticaria and hypotension can be produced by rapid administration of opioids, muscle relaxants, or vancomycin, drugs commonly given during anesthesia. In Australia, the incidence of allergic reactions during general anesthesia has been reported to be between 1:5000 and 1:25,000, with a 3.4% mortality rate.[1] A study of 200,000 patients undergoing general anesthesia in France found an incidence of 1:4500.[2]

CLINICAL SIGNS AND SYMPTOMS

During the perioperative period, the only feature of anaphylaxis may be cardiovascular collapse or airway obstruction.[3] Sudden bronchoconstriction is recognized by increased airway pressures during positive ventilation. Cyanosis with oxygen desaturation may be noted. In 100 cases of generalized reactions during anesthesia, 68% had circulatory collapse, 55% had widespread flush, 26% had skin edema, 23% had bronchial obstruction, and 11% had cardiac arrest. IgE-dependent sensitization was found in 42% of cases.[4] Flushing always affected the entire body, but the edema affected mainly the face. In 20% of cases edema appeared only at the end of the anesthesia.

ASSESSMENT OF REACTIONS

During an anesthetic-related reaction, numerous factors make assessment difficult. Medications are generally given in quick succession. Draping may prevent detection of early signs, such as urticaria or angioedema. Features of the reaction can be delayed such that temporal relationships between drugs administered and the clinical reaction are unhelpful. Reactions caused by mast cell–mediator release can be confused with other causes of hypotension or increased resistance to airflow, such as myocardial infarction; cardiac dysrhythmia; drug overdose; pulmonary embolus; irritant-induced bronchospasm; misplaced, blocked, or kinked endotracheal tube; pulmonary edema; aspiration of gastric contents or foreign body; seizure disorder; hypoglycemia; and stroke. Other conditions that can mimic anaphylaxis in this setting include stress-induced systemic mastocytosis, hereditary/acquired angioedema, and surgical hypothermia in cold urticaria patients.[5]

CAUSATIVE AGENTS
Drugs

Thiopental, a short-acting barbiturate, was first reported to be associated with allergic reactions in 1939.[6] Estimates of reaction incidence range from 1:400[7] to 1:30,000.[8] A retrospective study of adults with a history of a generalized reaction during anesthesia found evidence of allergy to thiopental in 17 of the 27 adults studied.[9] Positive immediate skin test responses to thiopental have been reported, and a RAST is available.[10, 11] The RAST is less sensitive, making it problematic for screening. Technical difficulties include a high degree of nonspecific binding, inconsistent blocking with fluid-phase thiopental, and poor solubility of thiopental at physiologic pH. The high incidence of reactions to propanidid and althesin (alphalaxone/alphadolone) has resulted in discontinuation of their use.[12-14] Reactions were attributed to the solubilizing agent, cremophor EL (polyoxyethylated castor oil), by means of complement activation and subsequent mast cell degranulation. When cremophor EL was substituted for propylene glycol to solubilize diazepam, the reaction rate increased from virtually none to 1:1000.[15] Etomidate, an imidazole derivative, is structurally unrelated to any of the other intravenous hypnotics. It is solubilized in propylene glycol, and the incidence of immediate hypersensitivity reactions is 1 in 500,000.[16, 17] Ketamine, a phencyclidine derivative, has rarely been reported to cause reactions.[18]

Neuromuscular blocking agents

Succinylcholine is a short-acting, depolarizing muscle relaxant. Atracurium and vecuronium are intermediate duration, nondepolarizing agents. All presently available muscle relaxants can produce dose-dependent, nonimmunologic histamine release that is related to the rate of administration. D-tubocurarine appears to have the greatest potential for this type of affect.[19] Generalized reactions characterized by hypotension, urticaria, and bronchospasm have occurred after the administration of muscle relaxants. There is evidence, including positive skin, Pausnitz-Kustner,[20, 21] and RAST test results,[22] for an IgE-dependent mechanism in some cases.

RAST-inhibition studies with various compounds indicate that IgE antibodies are directed against the quaternary or tertiary ammonium ions present in muscle relaxants.[23] This probably explains the cross-reactivity present among the different agents. Because most muscle relaxants contain two ammonium ions, they can directly cross-link cell surface IgE and initiate mediator release from mast cells and basophils; they do not require preliminary binding to carrier molecules. Molecules with two ammonium ions that are four angstroms or less apart appear incapable of inducing histamine release.[24] Six angstroms or greater between ammonium ions appears to be the optimal length for direct cross-linking of mast cell surface IgE molecules. Muscle relaxants with a rigid backbone between the two ammonium ions (pancuronium and vecuronium) appear to be

less likely than flexible molecules (succinylcholine) to initiate anaphylaxis.

Muscle relaxants cross-react with compounds containing quaternary and tertiary ammonium ions that are found in many drugs, foods, cosmetics, disinfectants, and industrial materials.[25] Patients may become sensitized through environmental contact with these substances, and in one study sensitized individuals were shown to have higher total serum IgE.[26] Because 90% to 95% of anaphylactic reactions to muscle relaxants occur in women, it has been speculated that exposure to ammonium ion epitopes in cosmetics may elicit sensitization.[27]

Opioid analgesics

Generalized reactions to opioids are usually due to direct mast cell–mediator release rather than an IgE-dependent mechanism. Most opioid-induced reactions are not life-threatening and include hives, pruritus, or mild hypotension. Fentanyl has been reported to cause an anaphylactic reaction in one patient with a positive immediate hypersensitivity skin test response.[28] A generalized reaction to meperidine has been described in a patient who had a positive IgE meperidine RAST, but specificity was not confirmed.[29] Presumably, other opioids can elicit IgE-dependent reactions, but because they can cause direct mediator release as well, skin tests must be interpreted cautiously. Confirmation of specific IgE antibodies to opioids requires carefully performed in vitro tests.

Antibiotics

Antibiotics are commonly administered perioperatively and can cause allergic (e.g., penicillin) or nonallergic (e.g., vancomycin) reactions. Antibiotics are commonly used to irrigate wounds at the end of a procedure.[30] Two case reports suggested bacitracin used in this manner caused generalized reactions; however, skin tests and RAST were not done.[31, 32] Topical administration of bacitracin has been followed by anaphylaxis, with an IgE-dependent mechanism suggested by a positive Prausnitz-Kustner test result.[33, 34]

Protamine (see section on protamine)

Protamine, used to reverse heparin anticoagulation in cardiac-pulmonary bypass procedures and cardiac catheterization, may cause severe reactions, including urticaria, bronchospasm, hypotension, and death.[35] Diabetics who have had treatment with protamine-containing insulin are 40 to 50 times more likely to have a life-threatening adverse reaction to intravenous protamine.[36]

PERIOPERATIVE EXPOSURES OTHER THAN DRUGS
Latex (see section on latex)

Latex has been recognized as a potent allergen and should be considered as a possible cause of any reaction that occurs during anesthesia.[37-39] At high risk are

patients with spina bifida.[40] Risk factors for sensitization are a history of allergy, asthma, or multiple operations.[41, 42]

Also at risk are health care workers, rubber industry workers, gardeners, and individuals allergic to foods such as banana, avocado, and chestnut, which contain cross-reacting allergens.[43, 44] Patients who have systemic reactions to latex during anesthesia often have a prior history of contact urticaria or angioedema from rubber gloves, balloons, or condoms. The amount of latex protein in gloves can vary 400-fold. Thus reactions may depend on the specific product.[45]

Ethylene oxide

Ethylene oxide is used for gas sterilization of medical/surgical equipment. Anaphylaxis has been reported in patients undergoing hemodialysis or plasmapheresis where disposable parts were sterilized with ethylene oxide.[46, 47] In vitro test results for specific IgE antibodies are positive in most patients who have generalized reactions during hemodialysis.[48] Ethylene oxide, used to sterilize devices used during anesthesia such as heart bypass pumps, could potentially cause anaphylaxis.

Other agents

Blood transfusions may elicit reactions, which include pruritus, erythema, urticaria, fever, and noncardiogenic pulmonary edema (in the absence of fluid overload or cardiac dysfunction). These reactions have a reported incidence of 3% in patients receiving correctly typed and cross-matched blood.[49] The reaction rate for platelet transfusions can be greatly reduced by separating the cells from the plasma phase immediately before administration.[50] Plasma proteins and synthetic substitutes, such as dextran, gelatin, and hydroxy ethyl starch solution, rarely cause direct release of histamine.[51] Plasma protein fractions can activate the kallikrein-kinin system.[52] Human serum albumin may activate complement due to aggregates, which form during storage or heating required to kill viruses.[53, 54] Sodium caprylate, a stabilizer added to albumin may cause acute reactions.[55] Mannitol or other hyperosmotic agents can cause direct histamine release. Methylmethacrylate (bone cement), used during orthopedic surgery, has been associated with reactions, including hypotension, hypoxemia, noncardiogenic pulmonary edema and cardiac arrest, but an allergic mechanism has not yet been shown.[56-58]

DIAGNOSTIC TESTS
Skin tests

Skin tests with general anesthesia drugs are difficult to interpret because many of these agents cause direct histamine release. Nevertheless, reactions to thiopental and neuromuscular blocking agents can be IgE-dependent, and immediate hypersensitivity skin tests can be useful in assessing patients who have experienced reactions to these agents.[9, 59, 60] Suggested concentrations as skin test reagents for these and other agents used in the

TABLE. Concentrations of medications for immedicate hypersensitivity skin tests*

Medication	Suggested concentration for intracutaneous testing (mg/ml)†	
	Fisher[64]	Moscicki et al.[66]
Thiopental	0.25	0.20
Succinylcholine	0.05	0.02
Pancuronium	0.002	0.002
Tubocurarine	0.001	0.0003
Metocurine	—	0.002
Thioamylal	—	0.01
Methohexital	0.1	0.1
Diazepam	0.05	—
Decamethonium	0.001	—
Alcuronium	0.00	—
Gallamine	0.04	—
Atropine		0.0006
Neostigmine	0.0025	—
Protamine	0.001	—
Morphine	0.00001	—
Meperidine	0.005	—
Fentanyl		0.001
Lidocaine	0.01	—

*Negative control = normal saline; positive control = histamine at a concentration of 0.275 mg/ml.
†Using more concentrated solutions than those listed may lead to false-positive reactions. At times, it may be prudent to begin skin testing at 10:1000-fold more dilute solutions.

perioperative period are listed in the Table above. Skin testing to latex may also aid in the differential diagnosis of perioperative reactions.

In vitro antibody measurements

In vitro tests have been developed for some neuromuscular blocking agents, thiopental, protamine, ethylene oxide, and latex. If the results are negative, the possibility of anaphylaxis cannot be excluded. On the other hand, a positive test result can help to identify patients at risk. They can also be used to identify potential causes of intraoperative death.

MANAGEMENT

Management includes treatment of acute reactions and avoidance of future reactions.[61, 62] Once a reaction is noted, the anesthetic should be stopped as soon as possible. Treatment of the acute reaction is described in detail in Chapter VII. For anaphylactoid reactions, H1 and H2 antihistamines can be effective in reducing histamine-related manifestations.[63]

PREVENTION

In the medical history of a patient obtained before undergoing anesthesia, there must be a careful inquiry about possible predisposing factors, including known allergy or intolerance to drugs. Any past history of reactions during anesthesia or previous reactions to contrast media or latex should be elicited, as should

other predisposing conditions, such as mastocytosis or hereditary angioedema. Familiarity with abbreviations used in anesthesia records is helpful (e.g., STP = sodium thiopental, USX = succinylcholine, VEC = vecuronium, DTC = d-tubocurare, and PCB = pancuronium bromide). It may be useful to enlist the assistance of the anesthesiologist to obtain an accurate description of medications used during a procedure and the temporal relationships of the events. Relevant information includes a list of all medications used, indications for their use, doses, the temporal relationship between the administration of each agent and the reaction, exact manifestations of the reaction, and the occurrence of continued symptoms.

Several independent prospective evaluations of anaphylaxis during general anesthesia reveal that negative skin prick and/or intracutaneous tests were reliable predictors of a benign operative course.[64, 65] In these two studies, avoidance of drugs that elicited positive skin test reactions apparently prevented anaphylactic reactions in 68 of 69 patients during anesthesia. Nevertheless, other prospective trials are needed to confirm the practical usefulness of these tests.

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XX. Progesterone

SUMMARY STATEMENTS

- Unexplained episodes of anaphylaxis may be caused by unusual reactivity to progesterone. Anaphylactic symptoms tend to be premenstrual but may occur anytime during the menstrual cycle. In one report, lactation caused complete remission of symptoms.
- The pathogenesis of this disorder is unknown, but laboratory studies have shown that progesterone may either induce histamine release from basophils directly or make mast cells more susceptible to other mast cell degranulators.
- Treatment options include a leutinizing hormone-releasing hormone (LHRH) agonist analog (e.g., Naferelin) or oophorectomy in particularly resistant cases.
- A differential consideration that may be confused with progesterone-induced anaphylaxis is catemenial anaphylaxis, which is not related to progesterone reactivity. Anaphylactic symptoms occur during menses, and full recovery after oophorectomy has been reported.

Among the causes of recurrent anaphylaxis in females is an uncommon syndrome caused by hyperreactivity to progesterone. It should be suspected in any female who is menstruating or pregnant and experiencing unexplained recurrent episodes of anaphylaxis. Although the anaphylactic episode tends to be premenstrual, it may occur anytime during the menstrual cycle. This syndrome was first recognized in the evaluation of a patient who had unexplained recurrent anaphylaxis with total remission during lactation.[1] When the patient became pregnant, the frequency and severity of the attacks became worse. After delivery and the institution of breast feeding, she had complete cessation of the attacks. When lactation stopped and her menstrual cycle resumed, this patient had a recurrence of severe anaphylaxis, including laryngeal edema.

As part of her subsequent evaluation, she was provoked with both progesterone and luteinizing hormone-releasing hormone (LHRH), both of which induced anaphylactic events. Progesterone was suspected as the inciting agent because provocation with follicle-secreting hormone (FSH), LH, and estrogen were uneventful. She was treated with a long-acting analog of LHRH, which competes with LHRH at a receptor level in the pituitary gland. Treatment with an LHRH analog causes the pituitary gland to become unresponsive to endogenous LHRH, with subsequent reduction in the secretion of FSH and (LH), which in turn leads to a reduction in estrogen and progesterone secretion. LHRH analog-treated patients cease menstruating and enter a temporary state of menopause. This agent caused a complete cessation of her attacks.

After a period of time on an LHRH analog, this patient underwent an oophorectomy with sustained remission of her attacks, which was still the case at follow-up 5 years later.

To determine if other women with unexplained recurrent anaphylaxis might have progesterone-induced anaphylaxis, four women experiencing recurrent anaphylaxis were recruited into a 4-month, double-blind, placebo-controlled cross-over study of the effects of LHRH analog on their anaphylaxis.[2] All four women thought that their attacks occurred more frequently during the premenstrual portion of their menstrual cycle and that the attacks during these times were more severe. In preliminary screening of the patients, two of the women experienced systemic reactions after challenge with methylprogesterone and LHRH. Only one of the patients who experienced anaphylaxis after provocation had a positive skin test response to progesterone. These two women improved during treatment with an LHRH analog, whereas the other two women did not. Urinary histamine levels, which had been elevated before treatment, were reduced in the two responsive women but not in the unresponsive women. Both women who responded subsequently had an oophorectomy with complete remission of anaphylaxis.

Patients with idiopathic anaphylaxis that worsened during the luteal phase of the menstrual cycle did not release histamine after incubation with progesterone.[3] However, a subsequent report demonstrated significant progesterone-induced histamine release in a patient with documented anaphylaxis after challenge with both synthetic and natural progesterone products.[4] In addition, incubation of her basophils with progesterone appeared to augment anti-IgE induced histamine release.

To confirm progesterone-induced anaphylaxis, a controlled challenge may be necessary. After insertion of an intravenous line and with life-saving equipment immediately accessible, the usual approach is to inject progressively 1, 2, 5, 10, 25, and 50 mg of progesterone in oil in the arm every 60 to 90 minutes while keeping the patient under close supervision. Reactions usually are restricted to urticaria and flushing, although systemic anaphylaxis can occur.

Treatment choices include an LHRH analog or oophorectomy. Most of the patients treated with an LHRH analog had total remission of anaphylaxis. However, side effects such as loss of secondary sexual characteristics and osteopenia may limit long-term use of this agent.

One woman has been reported to have episodes of anaphylaxis only during menstruation (a low progesterone state), with full recovery after hysterectomy with oophorectomy.[5] This apparently represents a syndrome of catamenial anaphylaxis not caused by progesterone.

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XXI. Anaphylactoid reactions to fluorescein

SUMMARY STATEMENTS

- Anaphylactoid reactions may occur after intravenous administration of fluorescein, a yellow, water-soluble, dibasic xanthine dye used in the diagnosis and detection of chorioretinal lesions.
- The most common adverse reactions to intravenous fluorescein are nausea and vomiting, but anaphylactoid reactions resulting in death have also been reported. Although increase in plasma histamine and decrease in various complement components have been described after anaphylactoid reactions, the pathogenesis of these reactions is not known.
- Prophylactic regimens similar to those used for radiocontrast media should be considered in patients who have had a previous anaphylactoid reaction and in whom use of intravenous fluorescein dye is indicated. However, these have not been used in sufficient numbers of patients to provide a definitive recommendation.

Intravenous fluorescein has been used for the past 30 years to evaluate chorioretinal disorders. Topical fluorescein is generally used in the detection and diagnosis of corneal lesions. Anaphylactoid reactions have been described in association with intravenous administration but not with topical use. After oral administration of fluorescein, a marked reduction in reactions was reported.[1]

Sodium fluorescein is a yellow, water-soluble, diabasic acid xanthine dye, which exhibits a green fluorescent color at pH greater than 6. The usual adult intravenous dosage is 500 to 750 mg by rapid injection. Most reports suggest no significant correlation of adverse reactions with fluorescein concentration.[2] There is one report of a reaction to a toxic contaminant, dimethylformamide, present in an intravenous fluorescein preparation.[3]

The most common adverse reactions to fluorescein are nausea and vomiting, with an incidence reported between 1% and 10%.[2] Anaphylactoid manifestations include rash/urticaria (1.2%), laryngeal edema or bronchospasm (1/3800), cardiovascular events (1/5300), and death (1/220,000 procedures). These prevalence rates are largely based on retrospective surveys of ophthalmologists. Because about 200,000 fluorescein angiograms are done in the United States each year, compared with 8,000,000 radiocontrast studies, the prevalence of anaphylactoid reactions to fluorescein is lower than that reported for hyperosmolar radiocontrast media. In patients with previous reactions to fluorescein, the repetitive reaction rates are 31% for nausea, 10.6% for vomiting, and 5.6% for itching/hives.[4] Repetitive reaction rates for cardiovascular or respiratory reactions have not been documented.

Skin testing with fluorescein and fluorescein-conjugated human serum albumin has not been helpful in the diagnosis of fluorescein-induced anaphylactoid reactions.[5] In previous reports, Prausnitz-Kustner testing for the presence of allergic antibodies was also negative.[6] Histamine release has been suggested as playing a role in fluorescein-induced reactions. In one series, 66% of patients with adverse reactions to fluorescein demonstrated increased plasma histamine levels[7]; however, most of these adverse reactions were nausea and vomiting. In addition, 15% of patients without adverse reactions showed a rise in plasma histamine after intravenous fluorescein. In the same series total hemolytic complement activity, complement proteins C1q, C4, and C3; and factor B decreased in all patients given intravenous fluorescein (even those without adverse reactions).

On the basis of the similarities to radiocontrast media-induced reactions, several prophylactic regimens for fluorescein-induced anaphylactoid reactions have been suggested. Early reports recommended 50 mg diphenhydramine before fluorescein administration.[8] Because of failures with diphenhydramine alone, studies have used pretreatment with a combination of prednisone (50 mg given 18, 12, 6 and 1 hour before fluorescein administration), diphenhydramine (50 mg given orally 1 hour before fluorescein administration), and cimetidine (300 mg given orally 1 hour before fluorescein administration) with apparent success.[9] In a single patient, a revised prophylactic protocol consisting of prednisone 20 mg three times a day (on the third and second prestudy days), prednisone 50 mg (7 hours and 1 hour before the procedure), diphenhydramine 50 mg, and cimetidine 400 mg given orally 1 hour before the procedure was effective when a prior protocol of oral prednisone 50 mg (given 19, 13, 7, and 1 hour before the procedure) and diphenhydramine 50 mg given 1 hour before the procedure had failed to prevent urticaria in the same patient.[10] Obviously, the number of patients pretreated with these protocols is small, and the optimum regimen remains to be determined by larger controlled studies. Before a repeat fluorescein test is undertaken in a patient with a previous anaphylactic reaction to intravenous fluorescein, it should be determined whether oral fluorescein administration would supply the necessary diagnostic information. If not, a prophylactic regimen similar to the protocols described above should be considered.

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XXII. Seminal fluid

SUMMARY STATEMENTS

- Anaphylaxis caused by human seminal fluid has been shown to be due to IgE-mediated sensitization by proteins of varying molecular weight.
- 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.
- The diagnosis is confirmed by either skin or in vitro tests for serum-specific IgE, with proper reagents obtained from fractionation of seminal fluid components.
- Prevention of reactions to seminal fluid can be accomplished by barrier use of condoms.
- 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.

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.[1, 2] 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.[3-5] In rare cases, spermatozoa have been identified as the source of allergens inducing a cell-mediated reaction.[6] 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 (e.g., walnuts) or drug (e.g., penicillin) to which there is established sensitization in the female partner.[7, 8] Human anaphylaxis has also been described after repetitive coital exposure to canine seminal plasma.[9]

A detailed history is essential. Recurrent localized vulvar and vaginal burning, itching, and swelling after ejaculation often precede the initial anaphylactic episode. Anaphylaxis begins within seconds to minutes after ejaculation, and presents with a range of symptoms, including diffuse pruritus and urticaria; pelvic pain associated with uterine contractions; nasal symptoms, including rhinorrhea and sneezing; wheezing, dyspnea and/or laryngeal edema; and, rarely, hypotension and syncope. The effective prevention of reactions by correct use of condoms is a common feature. Failure of condoms to prevent anaphylaxis suggests either incorrect condom technique or concurrent sensitization to latex.[10]

Atopy appears to be the most consistent risk factor; many patients present with a history of allergic asthma or atopic dermatitis.[2, 6, 11] Anecdotal case reports of seminal fluid anaphylaxis have occurred postpartum, after gynecologic surgery, and after injection of anti-Rh immune globulin.[2] It has not been established if such events are coincidental or could somehow modulate immune tolerance, resulting in sensitization to seminal fluid proteins. Reactions have also been observed in women whose male partners have recently undergone prostatectomy or vasectomy.[12] Anaphylactic events have been reported in women with multiple previous sexual encounters or, in others, after the first coital act.[2] Postcoital allergic reactions are not specific to one partner and almost always recur with different male partners.

The diagnosis must be confirmed by demonstration of sensitization to seminal fluid proteins by in vivo and in vitro immunologic methods. Demonstration of elevated serum-specific IgE assays, with both positive and negative control sera, confirms sensitization.[5] On the basis of available data, in vitro tests (e.g., RAST and ELISA) of serum-specific IgE appear to be less sensitive than skin testing, which could be due to the lack of reliable test allergens.[2] Thus, a negative serologic test result for seminal plasma–specific IgE does not exclude sensitization.

Because sensitive specific IgE assays are not available, skin prick testing with whole human seminal plasma from the male partner is recommended for initial screening of suspected 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 for spermatozoa, which is then filter sterilized.[13] Skin prick testing should be performed with seminal fluid and with saline and histamine as control reagents. To control for irritant responses, the male donor is also tested. A positive response is defined as a wheal 3 millimeters greater than or equal to that produced by saline with a flare, and a concomitant negative response in the male donor. It should be emphasized that protein allergens contained in whole seminal plasma may 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 gel filtration (Sephadex G-100) of whole seminal plasma to isolate allergen-rich fractions.[13, 14] Percutaneous or intracutaneous responses to either whole or seminal plasma fraction have been detected in all reported cases of anaphylaxis.

TREATMENT

Consideration must be given to the psychologic impact 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.[15] Once the diagnosis is suspected, the patient must be advised to avoid coital exposure to seminal fluid. This can be achieved by either temporary cessation of intercourse, coitus interruptus, or the correct use of latex condoms. 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.[7, 8] 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 cream (8%) in preventing mild reactions, it remains to be proven whether these options are effective in the prevention of severe anaphylaxis.[16]

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. Five separate fraction pools, which correspond to five different absorption peaks, are collected by elution of whole seminal plasma over a Sephadex G-100 column.[4, 6, 13, 14] Fraction pools are concentrated, quantitated for protein, and filter sterilized. In vivo allergenicity is evaluated by endpoint intracutaneous threshold testing. Because of its known immunosuppressive properties, the first fraction pool representing the initial absorption peak should not be used. After obtaining informed consent, subcutaneous injections of allergenic fractions are administered by a rush immunotherapy program beginning with a concentration that is at least 2 log dilutions higher than the endpoint 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 immuno-

therapy has indicated that desensitization can be accomplished at the conclusion of the immunotherapy protocol. In highly sensitive patients, injections may only be advanced over a period of weeks to months. An intravaginal injection 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 to 3 times per week). Prolonged abstinence has resulted in loss of tolerance and recurrence of anaphylactic episodes.[4] If abstinence periods can be predicted, subcutaneous injections of relevant allergens may be resumed to prevent loss of tolerance.

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XXIII. Exercise-induced anaphylaxis

SUMMARY STATEMENTS

- Exercise-induced anaphylaxis is a unique form of physical allergy. Initial symptoms typically include fatigue, diffuse warmth, pruritus, erythema, and urticaria, with progression to angioedema, gastrointestinal symptoms, laryngeal edema, and/or vascular collapse.
- Factors that have been associated with exercise-induced anaphylaxis include medications (e.g., aspirin/other nonsteroidal antiinflammatory agents) or food ingestion before exercise.
- Patients with exercise-induced anaphylaxis may have a higher incidence of personal and/or family history of atopy.
- Exercise-induced anaphylaxis should be distinguished from other exercise-associated syndromes, such as cholinergic urticaria and exercise-induced asthma.
- Medications used prophylactically are generally not useful in preventing exercise-induced anaphylaxis.
- Exercise should be discontinued at the onset of symptoms of exercise-induced anaphylaxis, and for some patients, exercise should be avoided in the immediate postprandial period (4 to 6 hours after eating).
- The emergency management of exercise-induced anaphylaxis is the same as the treatment of anaphylaxis from other causes.
- Patients with exercise-induced anaphylaxis should carry epinephrine and should wear and/or carry Medic Alert identification denoting their condition.

Exercise-induced anaphylaxis is a unique form of physical allergy. Initial symptoms typically include fatigue, diffuse warmth, pruritus, erythema, and urticaria, with progression to angioedema, gastrointestinal symptoms, laryngeal edema, and/or vascular collapse. Symptoms can persist for 30 minutes to hours. Transient loss of consciousness occurs in about a third of patients because of vascular collapse, while stridor occurs in almost ⅔ of patients.

Jogging is a common activity precipitating attacks, but brisk walking, bicycling, racquet sports, skiing, and aerobic exercise may also be associated with such anaphylactic reactions.[1-3] In some patients exercise-induced anaphylaxis will only occur after ingestion of a specific food or medication, such as aspirin or other nonsteroidal antiinflammatory agents. Ingestion of these medications before exercise has been reported by 13% of affected individuals,[4] and their elimination may 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. In some patients, specific foods have been shown to trigger these reactions. Elimination of these foods may allow the patient

to exercise without developing anaphylaxis.[4-7] Similar to the reactions with aspirin and nonsteroidal antiinflammatory medications, these patients may ingest these foods without developing anaphylaxis if they do not exercise after eating them. Individuals who have exercise-induced anaphylaxis may have a higher incidence of a personal and/or family history of atopy.[1]

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, 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 to 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 exercise, as noted above, is characteristically associated with an elevation in the core body temperature without vascular collapse. However, in two of 16 patients who did not have punctate urticaria with elevation of core body temperature, a syndrome resembling exercise-induced anaphylaxis was seen with punctate urticaria progressing to collapse.[2] Unlike cholinergic urticaria, simply raising the core body temperature does not necessarily produce symptoms of exercise-induced anaphylaxis. In addition, these syndromes may 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 ingestants and any other factors that might precipitate an episode of anaphylaxis. Particular attention should be given to the antecedent use of aspirin or other nonsteroidal antiinflammatory agents.

Prophylactic use of H1 and H2 antihistamines has generally not been effective in preventing exercise-induced anaphylaxis.[3] However, in selected patients antihistamine prophylaxis may help reduce the frequency and/or intensity of attacks.[8, 9] In some affected individuals cromolyn sodium has been noted to mitigate exercise-induced symptoms.[10] However, prophylactic medications cannot be relied on to prevent exercise-induced anaphylaxis.

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 reduction in intensity or duration may 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 from 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, may also be required. H1 blocking agents may 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 times of exercise for self-administration in the event of symptoms.

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XXIV. Idiopathic anaphylaxis

SUMMARY STATEMENTS

- Patients who have idiopathic anaphylaxis present with the same constellation of symptoms that are seen in other types of anaphylactic/anaphylactoid reactions.
- Patients with idiopathic anaphylaxis should receive intensive evaluation, including a meticulous history with careful analysis of events surrounding the development of episodes of anaphylaxis.
- Clinical evaluation may indicate the need for specific laboratory studies, which may help to exclude an underlying systemic disorder (e.g., systemic mast cell disease or hereditary/acquired angioedema). Selective testing for specific IgE antibodies and carefully controlled challenge procedures may occasionally help to establish an etiology for recurrent episodes of anaphylaxis.
- The acute treatment of idiopathic anaphylaxis is the same as the treatment of other types of anaphylactic/anaphylactoid reactions. Various protocols have been developed for the prevention of idiopathic anaphylaxis, but the treatment (e.g., corticosteroids, β-agonists, and antihistamines) often requires individualization.
- Education and support of patients with idiopathic anaphylaxis is an essential part of the management program.

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. Over 350 patients with idiopathic anaphylaxis have been reported, primarily by one group of investigators.[1-5] Although most instances of idiopathic anaphylaxis have been reported in adults, a few pediatric patients. with idiopathic anaphylaxis have also been reported.[6]

Patients who develop idiopathic anaphylaxis present with the same constellation of symptoms that are seen in other types of anaphylactic/anaphylactoid reactions. These attacks occur with variable frequency. Fatalities have been reported in patients who have been diagnosed with idiopathic anaphylaxis.[7,8]

The diagnosis of idiopathic anaphylaxis is a diagnosis of exclusion. Patients with idiopathic anaphylaxis should receive intensive evaluation, including a meticulous his-

tory, with careful analysis of the events surrounding the development of episodes of anaphylaxis. Clinical evaluation may indicate the need for specific laboratory studies, which may help to exclude an underlying systemic disorder (e.g., systemic mast cell disease or hereditary/acquired angioedema). Selective testing for specific IgE antibodies and carefully controlled challenge procedures may occasionally help to establish an etiology for recurrent episodes of anaphylaxis.

The acute treatment of idiopathic anaphylaxis is the same as the treatment for other types of anaphylactic/anaphylactoid reactions. Various protocols have been developed for the prevention of idiopathic anaphylaxis, but the treatment (e.g., corticosteroids, β-agonists, and antihistamines) often requires individualization. It may be necessary, in some patients, to provide for them and instruct them in the use of injectable epinephrine. Some patients may require continuing treatment with systemic corticosteroids and have been described as having corticosteroid-dependent idiopathic anaphylaxis. Some patients may require alternate day or daily prednisone.

Because patients with recurrent unexplained anaphylaxis often become very apprehensive, education and psychologic support of such patients by physicians and other patients with idiopathic anaphylaxis is an essential part of their management.

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XXV. Prevention of anaphylaxis

SUMMARY STATEMENTS

- Major risk factors for anaphylaxis include a prior history of such reactions, β-adrenergic blocker or possibly ACE inhibitor therapy, and the multiple antibiotic sensitivity syndrome. Atopic background may 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.

- 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.

- Avoidance management should be individualized, taking into consideration factors such as age, activity, occupation, hobbies, residential conditions, access to medical care, and the patient's level of personal anxiety.

- Pharmacologic prophylaxis can be utilized to prevent recurrent anaphylactoid reactions to radiographic contrast material and fluorescein, as well as to prevent idiopathic anaphylaxis. Pretreatment with glucocorticosteroids and antihistamines markedly reduces the occurrence of subsequent reactions.

- 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.

- 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 sometime in the future, the desensitization process must be repeated. Oral graded challenge to medications, such as aspirin, sulfasalazine or allopurinol, may restore tolerance to anaphylaxis as long as the medication is administered on a continuous basis.

- Patient education may 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.

IDENTIFICATION OF RISK FACTORS

A detailed medical history is essential for determining risk factors. A prior history of anaphylactic/anaphylac-

toid reactions is a significant risk factor for recurrent anaphylaxis after repeated exposure to a specific causative agent. For example, insect sting anaphylaxis occurs in about 60% of individuals with a history of prior reactions and positive venom test responses.[1] Atopic individuals have a slightly higher incidence of systemic reactions from insect stings but not from penicillin.[2-4] Recurrent reactions to radiographic contrast media (RCM) occur in 17% to 60% of individuals who have had prior reactions to RCM in the absence of pharmacologic prophylaxis or use of hypoosmolar agents.[5] An increased risk of an anaphylactoid reaction to RCM is associated with the presence of asthma and atopy.[6, 7] In recent years a syndrome known as *multiple antibiotic sensitivity* has been described.[8] Women appear to be more likely to have this syndrome, and there is also a familial tendency to develop this disorder.[9] Patients with this syndrome are at increased risk of having anaphylaxis to other classes of antibiotic agents, even if they are structurally unrelated to the antibiotic that initially produced anaphylaxis. Major risks of anaphylaxis from allergen immunotherapy are severe asthma and symptoms at the time of the injection (see section on allergenic extracts). Treatment with β-adrenergic blocking agents can augment the severity of anaphylaxis and may also increase the incidence of such reactions.[10] In addition, there are data to indicate that patients receiving ACE inhibitors may be at increased risk for development of anaphylaxis, as well as being more refractory to treatment with epinephrine if anaphylaxis develops.[11] This database includes reports from France indicating that the relative risk of anaphylactoid reactions was at least 20 times higher in patients undergoing dialysis if they were receiving ACE inhibitors.[12, 13] It also includes reports from Germany describing patients with stinging insect hypersensitivity taking ACE inhibitors and receiving venom immunotherapy who had recurrent anaphylaxis either from immunotherapy or from sting provocation. These patients had significantly lower renin, angiotensinogen, angiotensin I, and angiotensin II levels than patients who did not have repeated episodes of anaphylaxis with immunotherapy or stings.[14-17]

Confirmation of suspected causes of anaphylaxis may be accomplished by either skin or in vitro allergy tests and consultation by an allergist/immunologist. In the case of high molecular weight allergens, skin or in vitro tests may be used, recognizing that in vitro tests are not as sensitive as skin tests. If skin tests are required, in some cases the testing reagents should be carefully titrated, starting at very dilute concentrations. The risk of penicillin anaphylaxis should only be evaluated by skin tests. If detection of specific causes is unsuccessful, a diagnosis of idiopathic anaphylaxis is appropriate.

AVOIDANCE MEASURES

Avoidance of exposure to the offending agent is the preferred preventive strategy in most cases. When foods have been incriminated, the possibility that additives, preservatives, spices, or flavoring agents might be the cause of the reaction must also be considered. Antibiotics should be used judiciously in patients with multiple antibiotic sensitivity. Drugs with probable cross-reactivity to the causative drug should also be avoided if possible. Occupational exposure to inhalants (e.g., latex or drugs) should be controlled. Measures to avoid insect stings may be helpful. Patients at risk for anaphylactoid reactions to RCM should be considered for lower osmolality RCM.[7] Prevention of anaphylaxis during the course of allergen immunotherapy has been discussed in more detail in the Allergenic Extracts and Immunotherapy section. Allergen immunotherapy should be approached cautiously in symptomatic asthmatic subjects and in asthmatic patients who have severe, uncontrolled asthma.[18] In situations where the risks appear to be greater than the possible benefits, allergen immunotherapy should be discontinued. Individualization of avoidance management is required. Age, activity, occupation, hobbies, residential conditions, access to medical care, and level of personal anxiety must be carefully considered in each patient. Special vigilance on the part of the child's parents is necessary in children who develop anaphylaxis. Occasionally, foods or medications may act as cofactors with exercise for development of anaphylaxis. Discontinuation of either cofactor may prevent anaphylaxis. Patients residing in remote areas where access to medical care is difficult require special consideration.

PHARMACOLOGIC PROPHYLAXIS

Pharmacologic prophylaxis can substantially reduce the risk of recurrent reactions to radiocontrast agents in individuals with a history of prior reactions. Pretreatment with glucocorticosteroids and antihistamines often reduces the occurrence of subsequent reactions (see section on Anaphylactoid Reactions to Radiocontrast Media). Similar preventive pharmacotherapy may be required to lessen the incidence and severity of idiopathic anaphylaxis and anaphylactoid reactions to fluorescein.

DESENSITIZATION AND IMMUNOTHERAPY

Allergen immunotherapy for stinging insect hypersensitivity should be recommended for patients with proven anaphylaxis to stinging insects, because there is 90% to 98% effectiveness in preventing reactions if the patient is restung, and the risk from venom immunotherapy is low.[19, 20] Desensitization to medications (e.g., penicillin, insulin, sulfa drugs, vancomycin, and several xenogeneic products) that have caused anaphylaxis may be necessary if use of that medication is essential and no substitute can be found.[5] In the vast majority of cases, this preventive treatment is successful. However, the effects of desensitization are temporary, and if the drug is required sometime in the future, the desensitization process must

be repeated. Oral graded challenge with medications (e.g., aspirin, sulfasalazine, isoniazid, or allopurinol) may also restore drug tolerance as long as the medication is administered on a continuous basis.

PATIENT EDUCATION

The physician and the patient should have a careful and detailed discussion about how to avoid anaphylaxis. Great care must be taken to explain that there are often hidden sources of allergens and that highly sensitive individuals may react to exquisitely small quantities of allergen. For example, milk may be contaminated with penicillin, and various foods prepared in restaurants may be contaminated with small amounts of proteins, such as peanut, milk, and egg or flavor-enhancing additives. In addition, patients must be warned about the possibility of allergenic cross-reactions. For example, patients allergic to penicillin should be aware that cross-reactions may occur with other β-lactam antibiotics.[21] Almost all yellow jacket venom–sensitive individuals are also allergic to hornet venoms.[22] Cross-reactions are very common among foods. For example, an individual allergic to parsley may also be allergic to carrots, celery, and anise. In some cases, inhalant or contact allergens, such as latex, may cross-react with foods, such as bananas, avocados, or potatoes. Latex-sensitive patients must be warned about the intraoperative risk of latex exposure.[23] Patients with idiopathic anaphylaxis require support and reassurance because they have considerable anxiety about the lack of ability to predict severe reactions. All patients with anaphylaxis should be carefully instructed about when and how to use self-administered epinephrine. It is advisable that patients with anaphylaxis either wear a Medi-Alert bracelet or carry a Medi-Alert card so that agents that have caused anaphylaxis in the past will be noted by medical personnel in the event that the patient is unconscious. Patients should also be educated about the benefits of avoidance measures.

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