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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