

ANAPHYLAXIS: A PRIMER FOR THE HEALTHCARE PROFESSIONAL

Definition

Anaphylaxis is a potentially fatal allergic reaction that can occur anywhere and at any age. It is associated with exposure to many substances, including foods, insect venoms, drugs, and latex. To improve patient outcomes, it is imperative that all health care professionals be aware of the associated risk factors, be able to rapidly identify the signs and symptoms, and be prepared to effectively screen, educate, and protect patients at risk.

Anaphylaxis is a severe systemic allergic reaction: it is a response to an allergen that generally affects the body as a whole. While some anaphylactic reactions involve one organ system, such as the respiratory tract, other reactions may affect multiple systems simultaneously (including the cardiovascular and gastrointestinal systems). An anaphylactic event is generally acute in onset, but depends upon individual patient sensitivity, the dose, and the route of administration of the allergen. Most reactions begin within an hour of exposure to the allergen. Some individuals experience symptoms within seconds, while others demonstrate symptoms hours after exposure. In general, it is believed that more severe reactions are more rapid in onset. The manifestations of anaphylaxis can range from relatively mild symptoms, involving only the skin, to life-threatening reactions, involving the respiratory and cardiovascular systems.

For 30 years, epidemiologic data regarding the incidence of anaphylaxis from all causes have been limited. This has resulted in the perception by many clinicians that anaphylaxis is rare. Although estimates of its occurrence are difficult to determine, specialists agree that the incidence of anaphylaxis is underreported and appears to be increasing. A recently published study indicates that as many as 41 million individuals in the United States are at risk; however, cases may go unreported as many affected individuals fail to inform their physicians about prior reactions. Confusion about the definition of anaphylaxis may also lead to underreporting, and mild reactions, involving hives and occurring without other manifestations, are not always recorded as anaphylaxis. More severe symptoms may be misdiagnosed as acute asthma or other respiratory emergencies. While there have been few reports of the overall prevalence of anaphylaxis, it has been estimated that 5% of adults may have a history of anaphylactic reactions.

Pathogenesis of Anaphylaxis

Most anaphylactic episodes are mediated by IgE antibodies; these are also known as Type I hypersensitivity reactions. Prior to the anaphylactic event, a sensitization stage must occur, during which the affected individual is first exposed to the allergen. This exposure results in subsequent production of specific IgE antibodies. A repeat exposure to the same allergen results in the development of the signs and symptoms of anaphylaxis. The initial meeting with the allergen produces no symptoms, but sensitizes the individual to future exposures. In this stage, the individual is exposed to a normally harmless substance, such as peanuts or shellfish that the body perceives as an allergen. IgE antibodies, produced by plasma cells in response to this exposure, attach to tissue mast cells and peripheral blood basophils of the body's immune system. At this point, sensitization is complete.

During subsequent encounters with the same allergen, the allergen cross-links to adjacent IgE molecules on the surface of the mast cells and basophiles. This induces an enzymatic cascade that causes the mast cells and basophiles to de-granulate, releasing a flood of histamine and other bioactive mediators, such as prostaglandins and various cytokines. Together, these chemicals induce the inflammatory response, producing increased vascular permeability, vasodilation, smooth muscle contraction, and myocardial depression, which are responsible for the clinical manifestations of hives, edema, bronchospasm, and shock.

Allergens causing IgE-mediated anaphylaxis are primarily proteins. Proteins present in foods, insect venoms, and latex are the most common causes of anaphylaxis occurring by this mechanism.

Anaphylactoid Reactions

Anaphylactoid reactions resemble anaphylaxis clinically, but are unique in that they are not mediated by IgE and may occur upon initial exposure to an allergen. Despite these differences, it has become common practice to use the term *anaphylaxis* to describe either clinical syndrome. Although IgE antibodies are not involved here, the mast cell can be induced to react by other mechanisms. These include activation of the complement system or direct stimulation of mast cells and basophils to produce a sudden, massive release of histamine and other mediators.

Anaphylactoid reactions following the administration of blood products occur as a result of immune complex formation and activation of the complement system. As by-products of an activated complement system, the protein fragments, C3a and C5a, act as anaphylatoxins because of their ability to trigger release of mediators from mast cells and basophiles. Although the exact mechanism of direct stimulation of mast cells and basophils

is unclear, exposure to various agents may result in mast cell de-granulation and symptoms of anaphylaxis. Agents such as radio-contrast media, opioids, and neuromuscular blocking agents have been associated with these direct effects.

Other causes for which the mechanism is unknown include NSAIDs and exercise. Again, reactions to these triggers do not require prior exposure, although patients with a history of reactions to radio-contrast media demonstrate a markedly increased risk of anaphylaxis upon subsequent exposure. The incidence of reactions to aspirin and other NSAIDs is approximately 1%, although aspirin intolerance may be present in up to 20% of asthmatics. The occurrence of exercise-induced anaphylaxis is intermittent and unpredictable; however, episodes tend to decrease or stabilize over time. These reactions may be associated with the ingestion of certain foods prior to or after exercise.

Often, the cause of an anaphylactic reaction is obvious. In some cases, however, no specific etiology can be determined, even after repeated episodes and extensive investigation. This is referred to as idiopathic anaphylaxis.

Symptoms

The clinical manifestations of anaphylaxis are the result of the effects of mast cell mediators on 1 or more of the 4 major organ systems involved in a reaction: the skin, the respiratory tract, the gastrointestinal tract, and the cardiovascular system. These organ systems are rich in mast cells and are highly sensitive to the effects of mast cell mediators.

The cutaneous manifestations of flushing, pruritus, urticaria, and angioedema are seen in the majority of cases of anaphylaxis. Flushing and pruritus are often the first signs observed, later progressing to include hives and angioedema.

In the upper respiratory tract, edema of the larynx, epiglottis, and surrounding tissues can cause severe and even fatal obstruction. Swelling of the lips and tongue may be severe enough to impair ventilation. The symptoms of rhinitis (e.g., pruritus, watery discharge from the nose and eyes) are common.

In the lower respiratory tract, bronchospasm may be associated with chest or throat tightness, hoarseness, shortness of breath, cough, and wheezing, especially in patients with underlying reactive airways disease. In fact, there is evidence that patients with asthma may be at highest risk of fatal food-induced anaphylaxis because of their increased risk of lower airway complications.

Gastrointestinal symptoms occur most commonly in food-induced anaphylaxis, but can occur with other causes as well. Oral pruritus is often the first symptom observed in patients experiencing food-induced anaphylaxis. Abdominal cramping is also common, but nausea, vomiting, and diarrhea are frequently observed as well.

The cardiovascular effects of anaphylaxis may be profound. Typically, tachycardia is present, occurring as a compensatory response to a decreased intravascular volume. However, bradycardia may also develop as a result of increased vagal activity or in patients with atrial conduction defects or those taking beta blockers. Hypotension and hypotensive shock occur as a result of peripheral vasodilation, increased capillary permeability, and intravascular volume losses. In addition, ECG changes may be observed, including arrhythmias and evidence of ischemia, and patients may complain of chest pain.

The most common symptoms were urticaria and angioedema, occurring in 88% of patients. The next most common manifestations were respiratory symptoms, such as upper airway edema, dyspnea, and wheezing. Cardiovascular symptoms of dizziness, syncope, and hypotension, were less common, but it is important to remember that cardiovascular collapse may occur abruptly, without the prior development of skin or respiratory manifestations.

Other symptoms of rhinitis, headache, substernal pain, and pruritus without rash were less commonly observed.

It is commonly believed that all cases of anaphylaxis present with cutaneous manifestations, such as hives or mucocutaneous swelling. But in fact, as previously mentioned, up to 20% of anaphylactic episodes may not involve these signs and symptoms on presentation for emergency care. Moreover, a survey of children with food-induced anaphylaxis showed that 80% of fatal reactions were not associated with cutaneous manifestations, but rather involved initial gastrointestinal complaints of abdominal cramping and vomiting. This is important, as many of the most severe cases of anaphylaxis may go unrecognized by emergency personnel, resulting in inappropriate treatment and adverse health outcomes.

Uniphasic and Biphasic reactions

The clinical course of anaphylaxis is variable, and depends on patient sensitivity and dose and route of administration of the allergen. We are most familiar with the uniphasic type of anaphylactic reaction where onset occurs in seconds to under an hour following allergen exposure and resolves within 4 hours with appropriate treatment. However, up to 20% of cases exhibit a biphasic pattern, in which recurrence of symptoms, or the appearance of new signs and symptoms, is observed several hours after the initial onset of the reaction. Signs and symptoms experienced during the recurrent phase may be similar, or worse than, those associated with the initial reaction. Since life-threatening manifestations may recur. The American Academy of Allergy Asthma and Immunology recommends patients experiencing anaphylaxis be observed in a hospital for at least 4 hours after the initial symptoms subside.

In still other individuals, a protracted syndrome may occur, lasting from hours to days in duration. Given these variations in clinical course, it is important that clinicians be particularly vigilant in these cases, as death can occur virtually at any time during this period.

Another widely held belief is that the severity of previous anaphylactic reactions will predict future episodes or that each consecutive episode will become progressively more severe. To be accurate, there is no predictable pattern with regard to the severity of future anaphylactic reactions. The severity of any reaction depends on the individual's degree of hypersensitivity and the dose of the allergen, neither of which is constant or predictable. In addition, a patient's response to a particular allergen may be exacerbated by poorly controlled asthma, exercise, or the consumption of alcohol.

Fatality Risk Factors

Data regarding fatalities associated with anaphylactic reactions are limited. It's estimated 500 and 1000 individuals die of anaphylaxis each year, and that the risk of death in those who experience such a reaction approximates 1%. It is clear that the risk for an increased severity of anaphylaxis or death may be related to alterations in the body's homeostatic mechanisms, as in patients receiving beta blockers, ACE inhibitors, or in the presence of underlying adrenal insufficiency. Beta blocking drugs or the presence of asthma may worsen the airway response to treatment and complicate resuscitative efforts. Moreover, epinephrine administration in the face of beta blocker treatment may lead to unopposed α -adrenergic effects and significant hypertension. Preexisting cardiac disease or the rapid intravenous infusion of an allergen may also be responsible for poor outcomes. Importantly, the failure to administer epinephrine immediately after the onset of anaphylactic symptoms has been shown to be an independent risk factor contributing to fatal outcomes.

Anaphylaxis via ingested triggers:

Food Allergy

Food allergy is the most common cause of anaphylaxis, accounting for 35% to 55% of cases. The prevalence of food allergy is highest in the first year of life. Overall, 6% to 8% of young children display food allergy in population studies employing oral food challenges. The susceptibility of infants is believed to be the result of immunologic immaturity and, to some extent, immaturity of the gut. Introducing solid foods to an infant's diet *after* 4 months of age has been shown to prevent some food allergy. As children mature the prevalence of food allergy declines. Oral food challenge studies in adults indicate 1% to 2% are affected by food allergies.

For both children and adults, the incidence of food allergy and anaphylaxis is increasing. More children are demonstrating peanut allergy, possibly due to early exposure through breast milk, as well as many environmental factors. More adults are reporting allergic reactions to foods, possibly due to a greater exposure to processed and foreign foods.

The incidence of food-related anaphylaxis is underreported for several reasons. First, anaphylaxis is not reportable by the CDC. In addition, many patients fail to recognize a particular food as the stimulus for a reaction, and, if the reaction was mild, may have self-medicated with over-the-counter antihistamines and never consulted a physician. If the patient did seek emergency medical care, there is a good chance that no follow-up with a primary care physician or an allergist was scheduled.

Food-induced anaphylaxis is caused by exposure to specific food proteins (but not carbohydrates or fats). Lifelong sensitivity to peanuts, tree nuts, shellfish, and fish accounts for 80% to 90% of life-threatening anaphylactic reactions. Reactions from these triggers tend to be more severe. Additional triggers include milk, egg, soy, and wheat. Fortunately, at least 85% of children outgrow their sensitivity to these foods.

After exposure to food triggers, initial symptoms may be limited to the oro-pharynx, and include sensations of tingling or itching of the mouth, swelling of the lips or tongue, and throat tightness. As one might expect, the GI tract is prominently involved; cramping abdominal pain is common, but nausea, vomiting, and diarrhea are also

observed. Further spread of the antigen through the blood results in effects on the skin (urticaria, angioedema) and the respiratory system (shortness of breath, stridor, cough, and wheezing). In the most severe cases, the cardiovascular system is involved with hypotension and cardiovascular collapse. Food-induced reactions are often not associated with cutaneous symptoms. Studies have shown 80% (or more) of patients experiencing fatal food-induced anaphylaxis had no evidence of skin involvement.

The increase in reports of fatal food anaphylaxis is important. Approximately 150 individuals in the United States die each year from these events, a number underestimated due to the exclusion of those who die before reaching a hospital or sudden deaths attributed to other causes. Death is usually caused by a known food allergen ingested away from home and the failure to administer epinephrine promptly. This may be due to a delayed recognition of the seriousness of the reaction and a “wait and see” approach during an insidious progression of symptoms to a severe and irreversible level and delay in administration of epinephrine.

In one study (Sampson et al) many cases of fatal food-induced anaphylaxis occurred in a biphasic clinical pattern. In these, mild oral and gastrointestinal symptoms occurred within 30 minutes of food ingestion. These symptoms resolved, only to be followed 1–2 hours later by severe respiratory symptoms and hypotension. Due to this potential, it is critical that patients with food-induced anaphylaxis be closely observed for a minimum of 4 hours following their recovery from the initial event on a hospital setting.

Risk Management for Food Allergy

Strict adherence to prevention guidelines is the key to reducing risk for future anaphylactic episodes. Educating parents on the importance of avoiding trigger foods by reading food labels and learning ingredient terminology is vital. Learning alternative names for certain ingredients, e.g., whey for milk protein or natural flavor for cow’s milk, is a challenge but necessary. Patients and their families, friends, and teachers must be alert to changes in product labeling. They should be cautious of unknown ingredients to avoid potentially serious and unexpected reactions. Read labels thoroughly for the presence of “hidden” ingredients. Peanut-allergic patients must be educated to avoid certain high-risk foods, such as baked goods and Asian dishes, which may be prepared with nut-based ingredients. Children should be reminded frequently not to trade or share food, food utensils, or food containers. Even minute amounts of certain foods, such as peanuts, can be life-threatening when ingested by an allergic individual. Some children may experience a skin rash or an upset stomach simply as a result of exposure to residual peanut butter or milk on tables wiped clean of visible material, and others might have a fatal reaction. The Food Allergy & Anaphylaxis Network and The Asthma & Allergy Foundation of America, Texas have educational materials geared to patient education of food allergens.

Another important component of anaphylaxis prevention is risk management. Complete avoidance is impossible due to hidden ingredients or accidental exposure, so it is important that family, friends, and teachers be aware of a child’s allergic history and the potential ramifications associated with exposure. Guardians and caregivers must always be prepared to treat a reaction. An emergency plan should be in place in the home, at school, at day care, and during sports activities. Since the immediate administration of epinephrine may save a life, an auto-injector should be readily available, not locked in a nurse’s station. Teachers and other caregivers should be instructed on the proper use of the epinephrine device, as well as the importance of rapidly transporting the patient to a health care facility for emergency medical care. Patients should be urged to wear a medical alert bracelet in the event they are unable to communicate the nature and suspected cause of symptoms.

Anaphylaxis via injected triggers:

Stinging insect Venom

Systemic reactions to insect stings are a major medical problem. Studies indicate the incidence of systemic reactions from stinging insects of the Hymenoptera order ranges from 0.5% to 5%, meaning that up to 13 million Americans are sensitive to the venom of stinging insects. Many of these patients have reactions severe enough to warrant emergency care or hospital admission.

The actual incidence of these reactions is likely to be much higher, since reactions to insect stings are not reportable by the CDC, and few individuals report the event to their primary care physician or allergist. The incidence is also believed to be rising due to a recent influx of fire ants and, possibly, as a result of the presence of Africanized bees in southern Texas plus a greater interest in outdoor activities, such as gardening, hiking, camping, and bicycling in the rural countryside. It’s estimated approximately 40–100 deaths occur each year as a result of anaphylaxis due to insect stings, but again, since these are often unrecognized and rarely reported, this incidence is likely to be significantly underestimated. Anaphylaxis can occur in any age group, but most deaths due to insect sting anaphylaxis occur in adults.

The protein component of insect venom is responsible for the symptoms associated with anaphylaxis. Insects most commonly associated with triggering severe allergic reactions are members of the Hymenoptera order. These include bees, wasps, yellow jackets, hornets, and fire ants. Honeybees and yellow jackets account for

most of the systemic sting reactions reported in the eastern, mid-western, and western United States while wasps and fire ants cause most of the reactions in the southwestern and Gulf Coast regions of the country. As a result of warmer weather conditions, the fire ant has become an increasingly prevalent pest and common cause of venom-associated reactions. Known for their aggressive behavior, fire ants attack in swarms, stinging their victims up to 7 or 8 times. These insects pose a serious health risk to susceptible humans and animals.

Normally, an insect sting produces local pain, redness, and mild swelling for anyone stung. There is always pain, which differentiates stings from insect bites. This reaction usually subsides within 1 to 2 hours. Large local reactions are more pronounced and involve swelling extending from the sting site over a large area. Symptoms usually peak in 48 hours and may last up to 1 week. If severe, such reactions may be accompanied by fatigue and nausea.

Symptoms of venom-induced anaphylaxis vary from patient to patient and are typical of anaphylaxis triggered by other causes. The most common symptoms are cutaneous, including urticaria, flushing, and angioedema. Additionally, respiratory (upper airway edema) and cardiovascular events (shock) can be fatal. For most, symptoms occur within 15 to 20 minutes. For patients who have experienced venom-induced anaphylaxis and don't undergo venom immunotherapy, the risk of a systemic reaction (of equal or lesser severity) from future stings ranges between 30% and 60%.

Similar to the management of other causes of anaphylaxis, protection against future anaphylactic episodes requires both avoidance measures and risk management strategies. Avoidance is the primary preventive measure. However, accidents are never planned and not all stings can be prevented. Patients should be instructed to minimize their exposure to insects by having professionals remove any hives or nests; wearing white, smooth-finish clothes when at seasonal outdoor events; covering as much of the body as possible and keeping outdoor areas free of food refuse and garbage. They should avoid scented products such as perfumes, shampoos, or lotions when planning an outdoor event and should avoid wearing bright colors which attracts insects. Shoes should be worn at all times when outdoors. And finally, patients should be advised to avoid drink containers that do not allow content visibility to decrease the likelihood of a sting to the tongue or throat by a hidden insect. They should opt for bottled rather than canned drink products outdoors. Because insect stings cannot be completely avoided, all patients at risk for anaphylactic reactions should have an epinephrine auto-injector immediately accessible.

Those allergic to insect venom have the option of undergoing immunotherapy. Venom immunotherapy is medically indicated in any adult or child with a history of a systemic reaction to an insect sting. A positive skin test response to one or more insect venoms is required before immunotherapy is initiated. Venom immunotherapy has been shown to be 97% effective in providing protection against future systemic reactions related to insect stings. This is in contrast to the 30% to 60% risk for the development of a similar reaction that may occur in susceptible individuals not receiving immunotherapy. Most patients are able to discontinue venom immunotherapy after 3 to 5 years, although longer treatment may be recommended for patients experiencing more severe sting reactions. It must be remembered that, even after discontinuing venom immunotherapy, patients have a 10% risk of developing a systemic reaction to subsequent stings, although these reactions are generally mild.

Patients at greatest risk for systemic reactions related to immunotherapy include those with steroid-dependent asthma, a prior history of systemic reactions to immunotherapy, increased allergy sensitivity during diagnostic testing, and those receiving beta blocker or ACE inhibitor treatment. To ensure patient safety, immunotherapy must be performed only by a physician specifically trained in immunotherapy and anaphylaxis management and in facilities equipped to handle potential complications. Epinephrine should be immediately available during all immunotherapy sessions. Its recommended patients be closely monitored for at least 20 minutes following immunotherapy for any allergic reactions. This time may be extended to 30–45 minutes for high-risk patients. As insurance, physicians should consider prescribing epinephrine auto-injectors for patients with a significant risk for a systemic reaction following treatment. For patients undergoing venom immunotherapy, the incidence of allergic reactions is approximately 10-15% and these are mostly mild and tend to occur early in treatment. More severe reactions are much less common (2%–5).

Medication

Virtually any medication can cause anaphylaxis. The most common drug allergens, which occur as haptens, include antibiotics (beta-lactams, sulfonamides, vancomycin, ciprofloxacin, tetracyclines, nitrofurantoin), chemotherapeutic agents (vincristine, methotrexate, fluorouracil), aspirin and other non-steroidal anti-inflammatory drugs and biologicals such as vaccines and monoclonal antibodies but many other drugs can cause severe allergic reactions. It has been estimated that 1 in 2700 hospitalized patients experience drug-induced anaphylaxis and a recent meta-analysis of serious and fatal drug reactions indicates that, in the United States, as many as 500,000 hospital admissions per year may be associated with serious drug-related allergic reactions.

Penicillin is the most frequent drug-related cause of anaphylaxis, accounting for 75% of anaphylactic deaths in the United States.

Radio-contrast media (RCM) are used in more than 10 million procedures annually in the United States. Anaphylactoid reactions are estimated to occur in 0.22% to 1% of patients exposed. Patients with a history of such reactions have a 16% to 44% risk of reaction upon re-exposure. This risk may be reduced with pretreatment or the use of lower osmolality agents.

Anaphylaxis triggered through contact agents:

Latex

Latex allergy is recognized as a growing medical problem since the mid-1980s when surgical glove use rose dramatically to protect the health care work force against blood-borne pathogens associated with HIV. Recent reports indicate latex allergy affects between 1% and 6% of the general population, or as many as 16 million Americans. Among health care workers, this figure rises to between 8% and 17%, involving up to 935,000 medical personnel. As for other triggers, repeated exposure increases the risk of developing latex sensitivity. Those who have chronic medical conditions (e.g., congenital urinary tract problems, spina bifida) that involve repeated, ongoing exposure to latex are at higher risk for developing anaphylaxis. It's been reported as many as 67% of children with spina bifida exhibit some degree of latex sensitivity.

Latex-induced anaphylaxis is a response to the proteins present in natural rubber latex. Synthetic latex rarely causes allergic reactions. Natural rubber latex is a component of an estimated 40,000 common items, including rubber bands, elastic (e.g., in undergarments) and hospital and dental equipment. Latex-dipped products, such as balloons, gloves, condoms, diaphragms, bandages, baby bottle nipples, hot water bottles, pacifiers, and rubber toys are common culprits in triggering allergic reactions. Certain foods such as bananas, avocado, chestnuts, kiwi, and stone fruit (B-A-C-K-S) display a cross-sensitivity in latex-allergic individuals.

Three types of reactions may occur in individuals exposed to latex-containing products. It is important to distinguish them so anaphylactic reactions can be recognized and treated promptly.

- ▶ Irritant contact dermatitis is the most common reaction to latex; this involves the development of dry, itchy, irritated areas on the skin, usually the hands. It is caused by exposure to gloves and glove powder, workplace chemicals and frequent hand washing. Irritant contact dermatitis is not considered a true allergy.
- ▶ Allergic contact dermatitis is a delayed hypersensitivity reaction resulting from exposure to chemicals added to latex during harvesting, processing, or manufacturing. The skin reaction resembles that caused by poison ivy, occurring 24 to 48 hours after contact and may progress to oozing skin blisters or may spread away from the area of initial contact.
- ▶ Latex allergy is an immediate hypersensitivity reaction of potentially greater severity. Prior sensitization to latex proteins results in symptoms that range from mild (skin redness, hives, or itching) to moderate (rhinitis symptoms) to severe (wheezing, dyspnea). The greatest risk for these reactions is associated with mucosal contact.

To be most effective, prevention requires both avoidance measures and risk management strategies. Patients with a history of prior allergic reactions to latex should use latex-free products in the home and workplace. Because latex is a component of many household items, it may be difficult to avoid completely. However, as health care facilities, manufacturers, and others recognize the significant increase in reactions to latex, latex substitutes—or, at least powder-free, low-protein latex products—are becoming more readily available.

Latex-sensitive individuals should alert their employers and health care providers of their history so that latex-free products can be utilized and serious anaphylactic reactions avoided. These individuals should be encouraged to wear a medic alert bracelet and patients need to be educated regarding the potential cross-sensitivity between latex allergy and sensitivity to certain foods (B-A-C-K-S).

Additional Anaphylaxis Triggers

Exercise-induced anaphylaxis may be associated with ingesting food or medication (aspirin, NSAIDs) prior to physical exertion and may be associated with a higher incidence of familial atopic disorders.

In a substantial percentage of cases, no cause for anaphylaxis can be identified. In a retrospective review of 266 cases referred to a private allergy practice, Kemp and colleagues classified 37% (or 98 patients) as having anaphylaxis of an idiopathic etiology.

Diagnosing Anaphylaxis

Healthcare providers must obtain a careful history to identify potential causes for the anaphylactic event. The diagnosis of anaphylaxis may be confirmed by the presence of elevated plasma concentrations of the enzyme tryptase, which is specific for mast cell de-granulation. Tryptase may be a useful marker, as it remains elevated for up to 6 hours following an anaphylactic episode and is stable in refrigerated serum so an assay may be

performed in a previously obtained sample. Other laboratory data should be obtained to differentiate between anaphylaxis and other similarly presenting conditions.

In some cases, a definitive diagnosis of anaphylaxis can be made on the basis of clinical manifestations and evidence for a temporal exposure to a specific allergen. In general, the existence of airway compromise, hypotension, gastrointestinal symptoms, and generalized cutaneous reactions, alone or in combination, are essential to this diagnosis. The onset of symptoms is typically immediate, but in food allergies, can be delayed up to 1 to 2 hours after exposure.

Cutaneous and respiratory manifestations are most common with anaphylaxis but there may be a few important exceptions. In 2 studies of fatal, food-induced anaphylactic reactions, at least 80% presented without skin manifestations. This is an important point, as the diagnosis of anaphylaxis is most often overlooked in cases in which no cutaneous manifestations are observed. Similarly, cardiovascular collapse with shock may occur immediately without respiratory or cutaneous symptoms.

In other cases, anaphylaxis may be difficult to diagnose. Some conditions may share some clinical features of anaphylaxis, such as loss of consciousness and hypotension (as in vasovagal syncope) or generalized urticaria (seen in scombroid fish poisoning or systemic mastocytosis). These syndromes must be ruled out before a definitive diagnosis can be made.

Allergists routinely perform skin tests or RASTS (radio-allergo-sorbent tests) to identify the cause of a previous allergic reaction due to foods, insect venoms or drugs and guide further management. A wheal response indicates the presence of specific IgE antibodies to the allergen tested and identifies a specific trigger in a given patient.

Challenge testing may also be indicated. This involves a supervised exposure to suspected foods, drugs, or exercise by an allergist. In these situations, emergency medications (including epinephrine) and supportive care measures must be readily accessible since direct exposure may result in anaphylaxis.

Treatment and Prevention

Once anaphylaxis is diagnosed and treated, referral to an allergist is recommended so that allergy testing can be done to confirm the specific cause and provide specific information about treatment and prevention.

All patients at risk should be instructed as to the proper administration of epinephrine before the need for its use. Detailed instructions for self-administration (contained in each auto-injector package) should be carefully reviewed with the patient. In addition, a training device that simulates the auto-injection process without actual drug delivery is available for some auto-injectors. Using a trainer, patients should practice self-administration under the supervision of a physician (or a trained assistant) until they master an appropriate administration technique and feel comfortable administering epinephrine. Even so, this doesn't mean in an emergency, a patient can and will self-administer epinephrine.

Patients should be reminded to store their auto-injector in a dark place at room temperature: prolonged temperature extremes (refrigeration or car glove box, trunk) should be avoided for optimal functioning of the auto-injector. Patients should check their auto-injector monthly. If the unit has expired or the drug solution appears brown, the unit should be discarded and replaced immediately.

After using an epinephrine auto-injector, patients should be instructed to go immediately to the nearest Emergency Room for further medical attention. Medical personnel should be told that a dose of epinephrine has been given and they will dispose of the auto-injector properly. Due to the potential for a protracted or biphasic reaction, all patients should remain in the Emergency Department for observation for at least 4 hours.

Corticosteroids may be helpful in preventing prolonged or biphasic reactions and should be administered in all severe cases. If the initial reaction persists or escalates despite the initial dose of epinephrine, the dose may be repeated after 10-15 minutes. One study showed that 35% of patients required more than 1 dose of epinephrine to effectively manage an anaphylactic reaction. Basic supportive measures, such as oxygen and maintaining airway patency, may be required. Intravenous fluids or vasopressor therapy may be administered for hypotension. Patients receiving beta blocker therapy may be unresponsive to the vasopressor effects of epinephrine; in these cases, intravenous glucagon may reverse hypotension.

An additional dose of antihistamine should be given if symptoms persist and an H2 blocker such as cimetidine also may be helpful in reversing the histamine-induced component of anaphylactic hypotension.

Finally, follow-up care must be arranged prior to discharge. The patient should be referred to an allergist if they have not seen one previously. If this was a first reaction, the patient should be provided with an epinephrine auto-injector prescription and instructions regarding its use. The Emergency Room physician should make sure that patients who had previously been prescribed one have a current prescription.

Epinephrine Misconceptions

Misconceptions about epinephrine administration have resulted in delayed treatment and unfortunate outcomes. Some believe that epinephrine is too unsafe because of its adverse cardiovascular effects. These effects, which include hypertension, tachycardia, arrhythmias, and myocardial ischemia may be related to excessive α - and β -agonist activity associated with rapid intravenous infusion of moderate to high doses of epinephrine. The reality is that the danger of untreated anaphylaxis far outweighs the risks of epinephrine for the vast majority of patients, particularly when usual doses are administered by the subcutaneous or intramuscular routes. A study by Simons et al reported no serious adverse effects in pediatric patients receiving epinephrine by these routes. Increases in blood pressure and heart rate were observed, but were mild and transient and could not be correlated with serum epinephrine concentrations. Particular caution should be exercised, however, when epinephrine is administered to elderly patients or those with pre-existing cardiac conditions.

It is far better to use an epinephrine auto-injector when in doubt than not to administer the drug.

Given the life-threatening severity of anaphylaxis, it may be assumed that patients will seek medical care and inform their primary care physician of the event. The reality is that patients treated in the Emergency Department frequently don't seek follow-up care or referral to an allergist.

Patient Education

Once at risk patients are identified, they should be educated about anaphylaxis and appropriate avoidance measures:

- ◆ Physicians must emphasize that avoidance measures are not 100% effective in preventing future episodes. Accidental exposure can and will occur; therefore, patients need to be prepared
- ◆ Stress the importance of always having an epinephrine auto-injector on hand
- ◆ Stress that the expiration date of unit should be checked regularly
- ◆ Stress the need for immediate administration at the onset of symptoms. Provide training on the administration of an auto-injector
- ◆ To facilitate appropriate management, it may be optimal to supply some patients at risk with multiple units of auto-injectors particularly patients with severe prior reactions
- ◆ Explain the importance of follow-up care, including prompt transport to the nearest emergency care facility and referral to an allergist for further treatment
- ◆ Emphasize the patient's responsibility to report the details of any reaction to his/her primary care physician or allergist

Features of an Emergency Care Plan

Establishing an emergency plan involves identifying specific steps that parents and other caregivers can take to facilitate prompt treatment of an anaphylactic episode. This emergency plan is particularly useful in reducing associated fears and allows prompt action to potentially save a life. Since symptoms can escalate quickly to life threatening, epinephrine auto-injectors should be administered (through clothing if necessary) into the thigh area immediately at the onset of symptoms. A caregiver should then call for help (911, physician, parents) and the patient should be quickly transported to an emergency care facility for further treatment and observation. The patient should be kept warm, quiet and reassured that help is on the way. Specific guidelines for the administration of antihistamines should be provided; these drugs should never be considered a substitute for epinephrine in this situation. Patients and caregivers should be instructed to bring used auto-injectors with them to the Emergency Department.

INFORMATION COMPILED BY THE ASTHMA & ALLERGY FOUNDATION OF AMERICA, TEXAS



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