Urticaria, Angioedema, and Anaphylaxis

Urticaria, angioedema, and anaphylaxis are manifestations of the immediate hypersensitivity reaction. Immediate hypersensitivity is an antibody mediated reaction that occurs within minutes to hours of exposure to a particular antigen by an immune individual. Twenty percent of the population will have one of these manifestations, especially urticaria, at some time during life.

I. **Pathophysiology**

A. **Urticaria** (or hives) is an intensely itchy rash that consists of raised, irregularly shaped wheals. The wheals have a blanched center, surrounded by a red flare. Urticaria is caused by histamine release from dermal mast cells. Histamine release is most commonly caused by an immunologic reaction between antigens and IgE antibodies bound to mast cell membranes. Histamine causes increased vascular permeability. Antigens, chemicals and physical agents (detergents or ultraviolet light) can cause urticaria.

B. **Angioedema** is an area of circumscribed swelling of any part of the body. It may be caused by the same mechanisms that cause hives except that the immunologic events occur deeper in the cutis or in the submucosal tissue of the respiratory or gastrointestinal tract.

C. **Anaphylaxis** is the acute reaction that occurs when an antigen is introduced systemically into an individual who has preexisting IgE antibodies.

1. The patient has difficulty breathing from constriction of the major airways and shock due to falling blood pressure. The reaction occurs within seconds an hour of introduction of the antigen. These symptoms are caused by histamine release.
2. An anaphylactoid reaction is similar to anaphylaxis, but it is not immunologically mediated. Mannitol, radiocontrast material, and drugs (opiates, vancomycin) may degranulate mast cells and cause a reaction that resembles anaphylaxis.

II. **Anaphylaxis**

A. **Common causes of IgE-mediated anaphylaxis**

1. Insect venoms
2. Airborne allergens
3. Foods such as peanuts, eggs, milk, seafoods, and food dyes and flavors
4. Antitoxins to tetanus and other microbial products of animal origin

B. Low molecular weight chemicals may bind to host proteins and act as haptens in the production of IgE antibodies. These low molecular weight chemicals, such as drugs (particularly penicillins), are not in themselves immunogenic.

C. **Symptoms of anaphylaxis** include pruritus, injection of the mucous membranes, bronchospasm, and hypotension.

D. **Prevention of Anaphylaxis**

1. Anaphylaxis is best prevented by avoidance of the cause. However, anaphylaxis frequently is unanticipated. Individuals with a history of anaphylaxis should be provided with injectable epinephrine.
2. Short-term desensitization may be needed in a patient requiring antibiotic treatment. Desensitization is accomplished by injecting increasing doses of penicillin, every 20 minutes, over 8 hours, starting with 10 units and increasing to 1,000,000 units.
3. Long-term desensitization has a 90% success rate with bee venom and a 85% success rate for rhinitis due to inhalants. Desensitization to food allergens is very hazardous and should not be

attempted.

E. **Treatment of Acute Anaphylaxis**

1. Epinephrine in a 1:1000 dilution (1.0 mg/ml) should be injected at 10-20 min intervals at 0.01 mL/kg SQ per dose, with a maximum dose of 0.3 mL/kg per dose SQ.
2. Oxygen should be administered (100%, 4-6 L/min) and the airway secured.
3. Albuterol, 0.1-0.2 mL/kg in a 5 mg/mL solution, should be given via nebulizer every 4-6 hours.
4. Administration of diphenhydramine or chlorpheniramine and corticosteroids are secondary measures which should be considered when a complete response to epinephrine does not occur.

III. **Urticaria**

A. **Hives** most commonly results from ingestion of foods, food additives, or drugs. These usually cause hive formation for only a few hours to two days. Hives also may be associated with infections caused by parasites or viruses (eg, hepatitis or infectious mononucleosis). Hives may also occur in collagen vascular diseases, such as systemic lupus erythematosus.

B. **Cold urticaria** may be induced by exposure to cold, which may result in hypotension after immersion in cold water. The diagnosis is established by placing an ice cube on the forearm for a few minutes. A significant urticarial reaction within 4-8 minutes is diagnostic. Cyproheptadine in a total dose of 8 mg/m^2/day (2-4 mg every 8-12 hrs) is the treatment of choice.

C. **Cholinergic urticaria** is characterized by the appearance of small punctate wheals, surrounded by a prominent erythematous flare. These small papular urtications are pruritic and appear predominantly on the neck and upper thorax. The lesions often develop after exercise, sweating, exposure to heat, or anxiety. This type of urticaria is caused by stimulation of cholinergic fibers. Cholinergic urticaria is treated with hydroxyzine in a dose of 50-100 mg/day. Prophylactic treatment consists of hydroxyzine, 0.5 mg/kg every 4-6 hrs.

D. **Solar urticaria** may be caused by various wavelengths of light (280-500 nm). It is uncommon, and it is treated with sun screens.

E. **Chronic urticaria** is caused by ingestion of food substances that contain natural salicylates. Sensitivity to the food additive tartrazine yellow No. 5 frequently is found in patients with salicylate sensitivity. Chronic urticaria is treated with corticosteroids.

F. **Exercise urticaria** is characterized by hives and bronchospasm after exercise. Sometimes the recent ingestion of an offending food in combination with exercise will cause symptoms of immediate hypersensitivity.

G. **Genetic deficiencies of complement** factor H or factor I may cause urticaria. Patients who have these defects frequently develop severe hives, particularly after exposure to cold or hot water or alcohol ingestion. These rare defects are inherited as autosomal recessive traits.

1. The diagnosis is made by finding a low level of serum C3.
2. Treatment consists of nonsedating antihistamines such as loratadine or fexofenadine.

H. **Treatment of Urticaria.** Urticaria generally is a self-limiting disorder and usually requires only antihistamines. Hydroxyzine 0.5 mg/kg is the most effective treatment. Diphenhydramine 1.25 mg/kg every 6 hrs is also effective.

IV. **Angioedema**

A. Angioedema is mechanistically similar to hives, but the reaction occurs deeper in the dermis. It causes diffuse circumscribed swelling. Angioedema is often acquired, or it may be observed in an inherited disease known as hereditary angioneurotic edema (HANE).

B. **Hereditary Angioneurotic Edema**

1. HANE is characterized by episodes of localized subcutaneous edema of any part of the body.

2. Attacks of severe abdominal cramps and vomiting may be caused by edema of the bowel wall. It may lead to needless surgery if not recognized early.
3. Severe attacks of colic may occur during infancy.
4. Laryngeal edema may sometimes progress to total upper airway obstruction, pulmonary edema, and death. Attacks of palatal and laryngeal edema may follow dental trauma or occur during upper respiratory infections.
5. Almost all patients manifest symptoms of the disease during the first decade of life, but the symptoms become dramatically worse during pubescence and abate late in life. In young, adolescent women, the attacks of angioedema may occur around menstrual periods.
6. Angioedema does not itch; it causes a sensation of pressure because vast amounts of fluid may accumulate rapidly in a limb or external genitalia. The attacks generally last 24-48 hours and may be triggered by trauma, menstrual periods, extremes of temperature, fatigue, or stress.
7. HANE is inherited as an autosomal dominant disease. It never skips a generation. However, about 10% of cases are caused by new spontaneous mutations, which are passed to offspring.
8. Prophylaxis against attacks of angioedema can be achieved with impeded androgens (androgens that are only minimally virilizing).
    a. Stanozolol, at a dose of 2 mg/day; or danazol, 50-300 mg/day, can prevent attacks of angioedema.
    b. Other effective maintenance therapies include epsilon amino caproic acid and tranexamic acid, which inhibit plasmin activation for long-term prophylactic management.
    c. Preparations of C1 inhibitor purified, from human plasma have been used extensively in Europe. They are effective and provide immediate relief from severe abdominal symptoms.

C. **Acute treatment of angioedema** does not generally respond to epinephrine, antihistamines, or steroids. Treatments of angioedema consist of supportive therapy with IV fluids, analgesics, and airway management. Fresh frozen plasma is an alternative therapy which is generally effective. §