Chapter 65
Allergy and Immunology for the Internist

I. Basic Information

A. Definition of Allergens: Proteins of appropriate size that after inhalation, injection (e.g. drug, venom) or ingestion provoke an IgE antibody response and clinical symptoms in sensitive individuals. Common aeroallergens include trees, grasses and molds, as well as animals (domesticated pets; rodents), dust mites and cockroaches.

B. **Acute phase reaction**: Allergic response that begins within minutes of allergen exposure. Symptoms include pruritis and hives (skin), wheezing (lungs), rhinorrhea and sneezing (nose), erythema and tearing of eyes.

1. Allergen cross links specific IgE bound to the surface of mast cells and basophils
2. After surface IgE is cross-linked, mast cells & basophils release mediators, such as histamine (stored in cytoplasmic granules) and leukotrienes/prostaglandins (rapidly synthesized from arachidonic acid).

C. **Late phase reaction**: occurs four to twelve hours after acute phase and initial allergen exposure. Symptoms are similar to acute phase reaction, and mirror the inflammation seen in asthma and chronic rhinitis.

1. Pathogenesis includes leukocyte infiltration into tissues, which release Th2 cytokines (IL-4) and chemokines (chemoattractant cytokines).
2. Histamine levels also increase.

II. Clinical Presentation of Allergic reactions

A. **Anaphylaxis**: An IgE-related response, resulting in the rapid onset of systemic symptoms after exposure to antigen including pallor, pruritis, dyspnea, weakness, urticaria, wheezing, erythema, flushing, cyanosis, angioedema, diarrhea, nausea, vomiting, abdominal cramping and hypotension. (Some present with a biphasic illness, beginning with early abdominal symptoms before respiratory symptoms/vascular collapse set in). May be fatal due to upper airway obstruction or vascular collapse.

1. Mechanism: Mast cell and basophil mediators released by allergen binding IgE. Mediators released include histamine, platelet activating factor, prostaglandin D2, leukotrienes and cytokines (e.g. TNF-alpha and IL-1).
2. Causes of anaphylaxis include foods (especially nuts, shellfish, eggs or milk), exercise (generally in people with an allergic background), medications (see below), insect bites (for which immunotherapy is over 97% protective), and latex (an increasing phenomenon).
    a. Idiopathic anaphylaxis: 30 to 40 % of all recurrent anaphylaxis (a diagnosis of exclusion).

3. Cornerstone of treatment is avoidance of allergens. Treatment of an episode of anaphylaxis includes immediate treatment with epinephrine, followed by oxygen, antihistamines, corticosteroids, and beta-agonists (as needed) for support.

B. **Anaphylactoid Reaction**: a non-IgE triggered process that resembles anaphylaxis. May be caused by aspirin and NSAIDS (due to inhibition of cyclooxygenase), radiocontrast agents, and rarely, opiate drugs.

1. Symptoms from aspirin and NSAIDS include rhinoconjunctivitis, urticaria, bronchospasm, angioedema and laryngeal edema; treatment is avoidance or aspirin desensitization.
2. Symptoms from radiocontrast agents include the spectrum of symptoms seen with anaphylaxis
    a. Despite common belief, there is no relationship of radiocontrast allergy with allergy to fish, shellfish, or iodine allergy
    b. Pre-treatment regimen includes prednisone (50mg, administered at 13, 7, and 1 hour prior to procedure) and diphenhydramine (IM or PO) 1 hour prior to procedure.

C. **Urticaria and angioedema**:

1. Urticaria is characterized by well-circumscribed wheals from involvement of the upper layer of the dermis. Wheals are erythematous, with blanched centers, pruritic, and may occur anywhere on the body. Usually result from a type 1 hypersensitivity reaction.
    a. Lifetime risk of a single episode of acute urticaria very high (1 in 4 adults)
    b. Urticaria lasting more than six weeks is labeled chronic urticaria.
2. Angioedema: acute development of swelling and edema of submucosa or subcutaneous tissue; symptoms based on tissue involved. Typically non-pruritic.
    a. Occurs with urticaria in approximately 50% of chronic cases
    b. 10% of chronic cases have angioedema alone, 40% urticaria alone
3. Differential causes of urticaria or angioedema: drugs, thyroid, autoimmune (vasculitis), hepatitis, parasitic infection, food, infections (viral), malignancy, cryoglobulins. Physical triggers of urticaria may also exist, including cold, heat, pressure, and exercise.
    a. Persistent lesions(> 72 hrs) should be biopsied to exclude vasculitis
4. Mechanism unknown, may involve chronic mast cell degranulation. A subset of patients have antibodies against IgE or the IgE receptor.

5. Cornerstone of treatment is antihistamines. May add H2 blocker or tricyclic antidepressant (doxepin) for severe cases. Short-term oral corticosteroids also used for severe eruptions.

III. Clinical Presentations of Allergic and Immune-related diseases

A. **Allergic Rhinitis** (AR): allergen-induced inflammation of the lining of the nose characterized by nasal congestion, rhinorrhea, sneezing, itch and post-nasal drainage. The most common adult allergic disease (15% of U. S. population).

1. Overlap of symptoms with viral upper respiratory tract infection, nasal polyposis, non-allergic rhinitis with eosinophilia (NARES) and hormonally related nasal congestion (pregnancy, oral contraceptives, hypothyroidism).
2. Medications may also cause symptoms confused with allergic rhinitis, such as cocaine and beta-blockers.
   a. Rhinitis medicamentosa: overuse of OTC topical nasal decongestants
3. Other causes of symptoms that overlap with allergic rhinitis include vasomotor rhinitis (nasal congestion brought on by irritants such as cigarette smoke or cold air) and anatomic abnormalities (e.g. cerebrospinal fluid leak; deviated septum).

B. **Drug Allergy**: The majority of adverse drug reactions (ADRs) do not have an immunologic basis (<10% of all adverse drug reactions are immunologically based). The mechanism of many drug reactions is unknown.

1. Most drugs are small molecules that cannot act as an antigen unless modified.
2. Drugs may act as a hapten, in which the drug or its metabolite combine with a larger carrier protein and can thereby become immunogenic.
   a. Prior exposure is needed to generate an IgE antibody response
3. Time of onset from drug initiation assists in identifying allergic-type reactions:
   a. Immediate (<1 hour): pruritis, urticaria, rhinitis, wheezing, anaphylaxis.
   b. Accelerated (1-72 hours): urticaria
   c. Late (> 72 hours): maculopapular eruption, drug fever, hemolytic anemia, serum sickness, nephritis, leukopenias, exfoliative dermatitis, Stevens-Johnson syndrome
4. Penicillins and cephalosporins are the most common cause of immunologically based ADRs, typically acting as haptens. Cross-reactivity with cephalosporins is 6-30 % (2nd and 3rd generation cephalosporins are less likely to cross-react). Carbepenems (i.e. Imipenem) cross react with minor

determinants of PCN, while monobactams (i.e. Aztreonam) can be safely administered to PCN allergic patients

a. Other ADRs from penicillin include: antibody-mediated hemolytic anemia and thrombocytopenia; immune complex disease (characterized by fever, rash, glomerulonephritis and lymphadenopathy); cell-mediated contact dermatitis (with topical preparations); maculopapular rash seen in 5-13% of patients administered amoxicillin (incidence is increased with coincident EBV and CMV).

i. Basis of rash with amoxicillin is unknown; can often treat through the rash with close monitoring.

5. Sulfonamides are the second most common antibiotic class to cause drug reactions, usually via a T-cell mediated reaction. Seen frequently in patients with HIV.

C. **Allergic Skin Diseases**: Include hereditary and acquired angioedema, allergic contact dermatitis, and atopic dermatitis (Table 65-1).

D. **Immunodeficiency Syndromes**: Include immunoglobulin deficiencies, T and B cell deficiencies, as well as neutrophil and complement disorders.

E. Eosinophilia Syndromes

1. Churg-Strauss Vasculitis: a granulomatous vasculitis involving multiple organ systems, predominantly the lungs.

a. Patients present with severe asthma in the setting of systemic illness (fevers, malaise, weight loss), accompanied by pronounced eosinophilia.

b. Fleeting pulmonary infiltrates commonly seen on CXR.

c. Skin rash may also be seen; sinus involvement also described

2. Hypereosinophilic Syndrome

a. Systemic disorder characterized by dysfunction of several organs in the setting of persistent eosinophilia (>1500 cells/ml, for at least 6 months).

b. Diagnosis involves exclusion of other causes of eosinophilia

c. Cardiac involvement major cause of mortality

III. Diagnosis

A. Diagnosis of Allergic Rhinitis:

1. Clinical presentation often sufficient for treatment
2. Nasal secretion cytology: demonstrate predominance of eosinophils
3. Skin testing: search for specific IgE to allergens. Antihistamines must be avoided prior to skin testing.
4. RAST testing (Radioallergosorbent test): detects the presence of allergen-specific IgE in a subject's serum by in vitro assay
    a. An alternative to skin testing if patient must continue anti-histamines, but less sensitive than puncture skin tests.

B. Diagnosis of penicillin and related beta lactam antibiotic allergy:

1. 80-90% of penicillin "allergic" patients are not truly allergic; lack specific IgE
2. Skin test with major and minor determinants to detect presence of specific IgE
3. Skin test is not predictive for non-IgE dependent reactions (thus a negative skin test does not exclude a non-allergic adverse drug reaction)
4. Stevens-Johnson, exfoliative dermatitis are contraindications for PCN use

C. Diagnosis of Allergic Skin Diseases is often done based on the clinical presentation. Confirmation may be done with serum markers or skin testing (Table 65-1).

D. Diagnosis of Immunodeficiency Syndromes requires quantitative immunoglobulin levels or other serologic markers (Table 65-2).

E. Diagnosis of Eosinophilia Syndromes

1. Churg-Strauss Vasculitis is diagnosed by biopsy demonstrating granulomatous vasculitis in the patient with a compatible clinical presentation.
2. Hypereosinophilic Syndrome is diagnosed by organ biopsy demonstrating eosinophils and tissue damage in the patient with persistent eosinophilia (>1500 eosinophils/ml for at least 6 months), when other causes of eosinophilia have been excluded.

IV. Treatment

A. Allergic Rhinitis

1. Treatment should follow three-tiered approach:
    a. Avoidance or reduction of identified allergen triggers

b. Medications (See table 65-3)

i. Topical ocular agents (e.g. olopatadine; trade name Patanol) may be used for coexisting allergic conjunctivitis

ii. Leukotriene receptor antagonists are under study for use in allergic rhinitis

c. Allergen-specific immunotherapy: used in patients with severe AR that that is intolerant to or refractory to medications.

i. Mechanism of action unknown

ii. Treatment risks anaphylaxis; 20-30 minutes observation required after injection

iii. Maintenance dosing may be continued for 3-5 years

B. Drug Allergy

1. Treat with different drug class if possible

2. If no alternative antibiotic available, desensitization may be tried

a. Can be administered either oral or IV with increasing doses of drug

b. Theory is that it prevents anaphylaxis by favoring univalent haptens that do not cross link IgE and hence do not activate mast cells.

c. Duration of effect is limited to single treatment episode; must maintain uninterrupted treatment for duration of therapy

d. Future drug courses will require repeating the entire process

C. Allergic Skin Diseases: Treatment varies based on the underlying disorder (Table 65-1).

D. Immunodeficiency Syndromes: Treatment includes antibiotics for infection, with other treatment based on the underlying disorder.

E. Eosinophilia Syndromes

a. Churg-Strauss-high dose steroids and cyclophosphamide

b. Hypereosinophilic Syndrome

i. Corticosteroids

ii. Hydroxyurea

iii. Alfa-interferon

iv. Potentially monoclonal anti-IL-5

Suggested reading

1. The diagnosis and management of anaphylaxis, J Allergy Clin Immunol 101(6) part2:S465, 1998.

2. Primer on Allergic and Immunologic Diseases, JAMA 278 (22): 1799-2030,1997.

3. Middleton, Reed, Ellis, Adkinson et al: Allergy Principle & Practice, ed 5, St. Louis, 1998, Mosby.