K. J. Lee: Essential Otolaryngology and Head and Neck Surgery (IIIrd Ed)

Chapter 27: Immunology

Immunology is the study of the body's response to foreign substances.

An antigen is a substance which elicits a specific immune response, either production of antibody and/or activation of lymphocytes. Antigens are either proteins of high-molecular-weight carbohydrates. External antigens include microorganisms and pollen, while alloantigens are genetic, such as blood group (ABO and Rh) and tissue typing (histocompatibility) antigens.

An adjuvant is a substance that when mixed with an antigen will augment the immune response.

An antigenic determinant is the part of an antigen that induces the immune response.

A hapten is an nonantigenic substance that, when linked to carrier molecules, produces an immune response.

Components of the Immune Response

The major components of the immune response are lymphocytes, lymphokines, antibodies, macrophages, passively triggered cells, and nonspecific mediators such as complement and histamine (Fig. 27-1).

Figure 27-1. Components of the Immune Response

Bone Marrow Stem Cells

Thymus Processing

T Lymphocytes + Antigen

Sensitized T Cell

Memory cells
Lymphokine-producing cells
    Lymphokines
        Activated macrophage (antigen, complement, antibody)
Delayed hypersensitivity cells
    Cell-mediated immunity
Killer cells
    Cytotoxic reactions
Suppressor cells
Helper cells

Gut associated lymphoid tissue

B Lymphocytes + Antigen

Sensitized B cell

Lymphoblast
Plasma cell
Antibody
Memory cells

Null Lymphocytes + Antigen

Killer Cells

Cytotoxic Reaction

Lymphocytes

T lymphocytes are thymus influenced and compose 80% of the circulating lymphocytes. These cells are responsible for cell-mediated immune reactions, are inactivated by antilymphocyte serum, and usually are identified by rosette formation with sheep red blood cells. Subpopulations of T cells include:

1. Delayed hypersensitivity cells which are responsible for cell-mediated immune reactions.

2. Lymphokine producers which manufacture lymphokines, substances that influence effector macrophages.

3. Suppressor cells which retard antibody formation.

4. Helper cells which enhance B cell antibody production.

5. Killer cells which are cytotoxic to tumor cells and transplanted tissues.

B lymphocytes are derived from gut-associated lymphoid tissue and mature into plasma cells, the most important source of antibody. They compose 20% of circulating lymphocytes, contain surface immunoglobulin, and usually are identified by immunofluorescence with antiimmunoglobulin.

Null lymphocytes lack markers of both T and B cells and probably function as killer cells.

Lymphokines

These substances are soluble glycoproteins produced by sensitized T and B cells and have a molecular weight of 30.000-100.000:

1. Migration-inhibition factor (MIF).

2. Macrophage-aggregating factor (MAF).

3. Skin-reactive factor.

4. Cloning inhibitory factor.

5. Lymphotoxin.

6. Leukocyte inhibitory factor (LIF).

7. Chemotactic factor.

8. Blastogenic factor.

9. Interferon.

10. Lymphnode permeability factor.

11. Transfer factor (TF).

Of clinical importance are: (1) interferon which is produced locally in response to viral and parasitic infections and which renders transient protection against viral infections. Interferon also is being tested as an antitumor agent; (2) transfer factor which is useful for treatment of mucocutaneous candidiasis.

Antibodies

Antibodies are immunoglobulins that can react with the specific antigen that stimulated their production. Immunoglobulin molecules are all composed of light (small) and heavy (large) polypeptide chains consisting of a constant carboxyl terminal portion and a variable amino terminal portion (Fig. 27-2). Papain cleavage of an IgG molecules produces two Fab fragments which bind antibody and one Fc fragment which fixes complement and binds to cell membranes.

There are two types of light chains, kappa and lambda, present in all types of immunoglobulins. Each of the five types of immunoglobulins has a distinct class of heavy chain. Properties of the five types of immunoglobulins are listed in Table 27-1.

Table 27-1. Immunoglobulins

	IgG	IgM	IgA	IgE	IgD
Sedimentation constant	7S	19S	7S (serum) 11S (seretions)	8S	7S
Molecular weight	150.000	900.000	170.000 (se) 400.000 (secretions)	190.000	180.000
Serum concentration (mg/100 mL)	1000-1500	60-180	100-400	0.03	3-5
Heavy chain class	gamma	mi	alpha	epsilon	delta
Fixes complement	Yes	Yes	No	No	No
Crosses placenta	Yes	No	No	No	No
Comments	Major Ab late Ab response	Early Ab response	Main Ab in secret	Reagin Ab in allergy.	

Homogenous light chains (either kappa or lambda) are secreted in the urine as Bence Jones proteins in multiple myeloma. Light chains also are found in the amyloid of primary amyloidosis.

Waldenström's macroglobulinemia is associated with IgM immunoproliferations.

Heavy chain fragments are found in the urine and serum of individuals with heavy chain disease.

Macrophages

Macrophages and their circulating form, monocytes, constitute the mononuclear phagocytic system formerly called the reticuloendothelial system. These cells have an active role in the immune response. They process antigen for T and B cell recognition and they are activated by lymphokines and lymphocytes to enhance their phagocytic and digestive capacity.

Complement

The complement system is a complex system of 11 major proteins naturally occurring in serum which helps mediate immune and inflammatory reactions. This system can be activated by antigen-antibody complexes (classic pathway), or by a variety of substances such as bacterial lipopolysaccharides (properdin or alternative pathway). The major functions of complement are: (1) immune adherence (C3b); (2) anaphylatoxin production (C3a, C5); (3) chemotactic (C3a, C5a, C5b,6, 7); (4) lysis (C6,7,8,9).

Hereditary angioneurotic edema is an hereditary deficiency (autosomal dominant) of C1-esterase inhibitor resulting in episodes of increased C1 activity, particularly following trauma.

Consumption of C2 and C4 occurs resulting in release of a vasoactive kinin responsible for the edema. Life-threatening laryngoedema can result. Severe gastrointestinal

pain is common. This condition does not respond to epinephrine or corticosteroids and should be prevented with epsilon-aminocaproic acid or danazol.

Passive-cells include neutrophils, eosinophils, and basophils. Neutrophils are the major phagocytes in the circulation and clear antibody-coated microbes from blood and tissue.

Eosinophils and basophils are important in type I hypersensitivity reactions. IgE antibody can fix to these cells and cause release of mediators of anaphylaxis.

Hypersensitivity Diseases

There are four basic mechanisms of immunologic injury (Table 27-2).

Table 27-2. Immune Tissue Injury

	Type I Anaphylactic Atopic	Type II Cytotoxic	Type III Imune Complex	Type IV Delayed Hypersensitivity
Immunogl	IgE	IgG	IgG, IgM	None
Complement mediated	No	Yes	Yes	No
Mechanism	Mast cell degranulation	Complement cytolysis	Immune complex deposition	T cell lymphokine release
Examples	Anaphylaxis Rhinitis Asthma	Transfusion Rh reaction	Serum sickness Poststrep GN	Contact dermatitis Tuberculin.

Type I

Anaphylaxis or immediate hypersensitivity is usually mediated by IgE antibody which fixes to mast cell membranes and, in the presence of antigen, causes degranulation of the cell and release of mediators (Fig. 27-3). Intracellularly, the IgE activated membrane results in flow of calcium ions and microtubule aggregation. There is a decrease in the ratio of intracellular cyclic AMP to cyclic GMP. Agents capable of increasing cAMP inhibit histamine release.

Type I reactions cause anaphylaxis and allergic reactions to foods, drugs, pollens, and other inhalants, as well as allergic asthma and sinusitis. Atopic individuals have a genetic predisposition to form IgE-type reactions and comprise 15-20% of the population.

The mediators released by type I reactions are:

1. Histamine, which increases vascular permeability, causing tissue edema, and which causes contraction of smooth muscle resulting in pain and itching.

2. Slow-reacting substance of anaphylaxis (SRS-A), which causes smooth muscle

contraction and bronchial asthma.

3. Eosinophilic chemotactic factor of anaphylaxis (ECF-A), which causes local accumulation of eosinophils.

4. Serotonin, which acts in a similar manner to histamine.

5. Bradykinin, which causes prolonged smooth muscle contraction as well as vasodilatation.

6. Platelet aggregation factor (PAF), which aggregates platelets and causes them to release vasoactive amines.

7. Prostaglandins F and A, whose role is uncertain.

8. Anaphylatoxins, which cause histamine release from mast cells.

Modulators of type I reactions:

1. Atropine blocks formation of cGMP.

2. Methylxanthines prevent cAMP destruction.

3. Corticosteroids inhibit histamine formation and stabilize cell membranes preventing mediator release.

4. Catecholamines block alpha and beta receptors to permit accumulation of cAMP.

5. Antihistamines block histamin receptors on nerve endings.

6. Cromolyn sodium stabilizes cell membranes and prevents calcium influx.

Type II

Cytotoxic reaction occurs when IgG or IgM antibody reacts with antigens on cell surface membranes leading to cell lysis or damage. The Fab end of the antibody fixes to either natural or foreign antigen of the cell surface while the Fc end combines with either a monocyte or with complement to cause cell damage. Examples of type II injury are hemolytic anemia and immune leukopenia and thrombocytopenia.

Type III

Immune complex-mediated injury occurs when IgG or IgM antibody forms soluble complexes with antigen and settles out in endothelial surfaces of blood vessels, glomeruli, and synovium. Examples of type III injury are the Arthus reaction, serum sickness, and poststreptococcal glomerulonephritis.

Type IV

Cell-mediated injury occurs when sensitized T lymphocytes react with antigen and release lymphokines. Contact dermatitis is an example of type III reaction as is the tuberculin skin test.

Clinical Allergy

The most common allergic problems seen in ENT practice are allergic sinusitis, rhinitis, and bronchial asthma. Seasonal symptoms usually are related to pollens or mold spores while perennial symptoms usually are due to house dust, animal dander, and household molds. In the Northeast and Midwest tree and grass pollens are present in the spring, and ragweed, the mold spores of Alternaria and Hormodendrum are present in the late summer and fall. Proteins of the house mite are the main antigen in house dust. Aspergillus and Penicillium are the most common household molds. Food allergies are probably also of importance, but scientific documentation of this point is not available. There is no evidence to support the notion of allergy to an individual's "own" bacteria or fungal flora.

Allergy Evaluation

Careful history of a patient's symptoms and the correlation with potential allergens is essential. Seasonal symptoms, frequent sneezing, coexistent conjunctivitis, family history of atopy, eczema, and copious watery nasal discharge are all suggestive of allergy.

Skin Testing and Other Tests

1. Intradermal testing with aqueous extract of antigen is the best method of substantiating a clinical diagnosis of allergy. Systemic reactions may occur with this method.

2. The scratch test and prick test are not as sensitive as the intradermal test, but often are used to define highly allergic individuals to prevent systemic reactions.

3. Conjunctival testing is very sensitive, but of limited clinical value.

4. The RAST test (radioallergosorbent) measures antigen-specific antigen in the serum and correlates well with intradermnal testing. It is of value for those patients who cannot undergo skin testing.

5. The RIST test (radioimmunosorbent) produces similar results.

6. Eosinophil count: Elevated blood eosinophil count or demonstration of eosinophils in nasal secretions suggest allergy.

7. Patch testing is used for diagnosis of contact dermatitis. Antigen is placed in contact with the skin for 24-48 hours to produce local dermatitis.

8. Pulmonary functions tests accurately quantitate airway resistance and subclinical bronchospasm. Challenge with inhaled allergen is sometimes useful to diagnose allergic

asthma.

9. Elimination diets are the only reliable way of diagnosing food allergy. Food groups such as dairy products, wheat, and yeast, may be eliminated on a trial basis with close observation of symptomatic changes.

10. Venom skin testing for stinging insect hypersensitivity is accurate, but must be done with extreme caution.

Of no proven value are provocative testing by the intracutaneous or the sublingual route or the titration method of Rinkle for determining the optimum dose of immunotherapy.

Immunotherapy

Subcutaneous injections of aqueous or alum-precipitated allergen in a schedule of gradually increasing amounts until a maintenance dose is achieved has proved of value in the treatment of pollen and dust allergy. This method of biweekly or monthly perennial treatment is called immunotherapy. High concentrations of extract to achieve a total preseasonal antigen immunization (>25.000 protein nitrogen units (PNU)) is required. Blocking IgG antibody is produced which competitively binds antigen to prevent binding to IgE and subsequent mediator release. Moreover, IgE production is decreased resulting in lower serum levels.

Immunotherapy with stinging insect venom is effective as opposed to treatment with whole body extract. This procedure must be done with caution.

Of no proven value are the Rinkle method of titrated injection, sublingual therapy, or bacterial vaccine injection.

Immunodeficiency Diseases

T Lymphocyte Deficiencies

DiGeorge's Syndrome or Thymic Hypoplasia

This disease is not genetic, but is due to abnormal embryogenesis of third and fourth pharyngeal pouches resulting in hypoplasia of thymus and parathyroids. Neonatal tetany, unusual facies, increased infections, and abnormal delayed hypersensitivity with normal immunoglobulins are characteristic.

Nezelof's Syndrome

This syndrome is an autosomal-recessive thymic hypoplasia with an isolated T cell defect, normal immunoglobulins, and susceptibility to fungal and Pneumocystis carinii infection.

Partial T Cell Loss

Mucocutaneous candidiasis is the most common example. Isolated T cell deficiency with no delayed hypersensitivity to Candida causes recurrent infection of mucous membranes and nail beds. Transfer factor is the treatment of choice.

B Lymphocyte Deficiency

Transient Hypogammaglobulinemia of Infancy

A normal infant is born with 90% of normal IgG and no IgM or IgA. The IgG level falls for the first 3 months of life. The condition is self-correcting.

Congenital Agammaglobulinemia

Sex-Linked (Bruton Type). This type affects boys only. All immunoglobulins are low and there are frequent bacterial infections. The T cells are normal. Treatment is with gammaglobulin.

Dysgammaglobulinemia. There is a selective absence of one class of immunoglobulin. IgA absence if the most common (1:1000 individuals). It is due to increased T suppressor cells and failure of B cell maturation. It is not sex-linked. IgA deficiency is associated with autoimmune diseases and some malignancies.

Acquired Agammaglobulinemia

This is often associated with malignancies of the reticuloendothelial system such as lymphoma and multiple myeloma.

Combined Immunodeficiency Disease

Sex-Linked Agammaglobulinemia

Boys only are affected with a variable degree of agammaglobulinemia. There is both T and B cell dysfunction, with a 2-year life expectancy.

Autosomal Recessive (Swiss Type)

Both sexes are affected. Viral, fungal, and bacterial infections are due to a severe T and B cell defect. Lymphopenia and hypoglobulinemia are characteristic.

Wiskott-Aldrich Syndrome

This syndrome is X-linked with eczema, thrombocytopenia, and infections. There is a low IgM level. Transfer factor and bone marrow transplantation are sometimes helpful.

Immunodeficiency with Ataxia-Telangiectasia

This is autosomal recessive with a variable pattern. IgA and IgE deficiencies are most common with a decreased T cell function. These patients develop progressive neurologic involvement.