10 - Immunology; Allergic Disorders

Chapter 125. Biology of the Immune System

Introduction

The immune system distinguishes self from nonself and eliminates potentially harmful nonself molecules and cells from the body. The immune system also has the capacity to recognize and destroy abnormal cells that derive from host tissues (see p. 1057). Any molecule capable of being recognized by the immune system is considered an antigen (Ag).

The skin, cornea, and mucosa of the respiratory, GI, and GU tracts form a physical barrier that is the body's first line of defense. Some of these barriers also involve immune functions and other active defenses:

- Outer, keratinized epidermis: Keratinocytes in the skin secrete antimicrobial peptides (defensins), and sebaceous and sweat glands secrete microbe-inhibiting substances (eg, lactic acid, fatty acids). Also, many immune cells (eg, mast cells, intraepithelial lymphocytes, Ag-sampling Langerhans' cells) reside in the skin.

- Mucosa of the respiratory, GI, and GU tracts: The mucus contains antimicrobial substances, such as lysozyme, lactoferrin, and secretory IgA antibody (SIgA).

Breaching of anatomic barriers can trigger 2 types of immune response: innate and acquired. Many molecular components (eg, complement, cytokines, acute phase proteins) participate in both innate and acquired immunity.

Innate immunity: Innate (natural) immunity does not require prior exposure to an Ag (ie, memory) to be effective. Thus, it can respond immediately to an invader. However, it recognizes mainly Ag molecules that are broadly distributed rather than specific to one organism or cell. Components include

- Phagocytic cells

- Ag-presenting cells

- Natural killer (NK) cells

- Polymorphonuclear leukocytes

Phagocytic cells (neutrophils and monocytes in blood, macrophages and dendritic cells in tissues) ingest and destroy invading Ags. Attack by phagocytic cells can be facilitated when Ags are coated with antibody (Ab), which is produced as part of acquired immunity. Ag-presenting cells (macrophages, dendritic cells) present fragments of ingested Ags to T cells (which are part of acquired immunity). Natural killer cells kill virus-infected cells and some tumor cells. Certain polymorphonuclear leukocytes (eosinophils, basophils, mast cells) release inflammatory mediators.

Acquired immunity: Acquired (adaptive) immunity requires prior exposure to an Ag and thus takes time to develop after the initial encounter with a new invader. Thereafter, response is quick. The system remembers past exposures and is Ag-specific. Components include

- T cells

- B cells

Acquired immunity derived from certain T-cell responses is called cell-mediated immunity. Immunity derived from B-cell responses is called humoral immunity because B cells secrete soluble Ag-specific Ab. B cells and T cells work together to destroy invaders. Some of these cells do not directly destroy invaders but instead enable other WBCs to recognize and destroy invaders.

Immune Response

Successful immune defense requires activation, regulation, and resolution of the immune response.

Activation: The immune system is activated when a foreign Ag is recognized by circulating Abs or cell surface receptors. These receptors may be highly specific (Ab expressed on B cells or T-cell receptors) or broadly specific (eg, pattern-recognition receptors such as Toll-like, mannose, and scavenger receptors on dendritic and other cells). Broadly specific receptors recognize common microbial pathogen-associated molecular patterns in ligands, such as gram-negative lipopolysaccharide, gram-positive peptidoglycans, bacterial flagellin, unmethylated cytosine-guanosine dinucleotides (CpG motifs), and viral double-stranded RNA. Activation may also occur when Ab-Ag and complement-microorganism complexes bind to surface receptors for the crystallizable fragment (Fc) region of IgG (FcγR) and for C3b and iC3b.

Once recognized, an Ag, Ag-Ab complex, or complement-microorganism complex is phagocytosed. Most microorganisms are killed after they are phagocytosed, but others (eg, mycobacteria) inhibit the phagocyte's ability to kill them once they are engulfed. In such cases, T cell-derived cytokines, particularly interferon-γ (IFN-γ), stimulate the phagocyte to produce lytic enzymes and other microbicidal macrophage products, which kill the microorganism.

Unless Ag is rapidly phagocytosed and entirely degraded (an uncommon event), the acquired immune response is recruited. This response begins in the spleen for circulating Ag, in regional lymph nodes for tissue Ag, and in mucosa-associated lymphoid tissues (eg, tonsils, adenoids, Peyer's patches) for mucosal Ag. For example, Langerhans' dendritic cells in the skin phagocytose Ag and migrate to local lymph nodes; there, peptides derived from the Ag are expressed on the cell surface within class II major histocompatibility complex (MHC) molecules, which present the peptide to CD4 helper T (T_H) cells. When the T_H cell engages the MHC-peptide complex and receives various costimulatory signals, it is activated to express receptors for the cytokine IL-2 and secretes several cytokines. Each subset of T_H cells secretes different substances, which effect different immune response (see p. 1081).

Class II MHC molecules present peptides derived from extracellular (exogenous) Ag to CD4 T_H cells; in contrast, class I MHC molecules present peptides derived from intracellular (endogenous) Ag (eg, viruses) to CD8 cytotoxic T cells. The activated cytotoxic T cell then kills the infected cell.

Regulation: The immune response must be regulated to prevent overwhelming damage to the host (eg, anaphylaxis, widespread tissue destruction). Regulatory T cells (most of which express Foxp3 transcription factor) help control the immune response via secretion of immunosuppressive cytokines, such as IL-10 and transforming growth factor-β (TGF-β), or via a poorly defined cell contact mechanism. These regulatory cells help prevent autoimmune responses and probably help resolve ongoing responses to nonself Ag.

Resolution: The immune response resolves when Ag is sequestered and eliminated from the body. Without stimulation by Ag, cytokine secretion ceases, and activated cytotoxic T cells undergo apoptosis. Apoptosis tags a cell for immediate phagocytosis, which prevents spill-age of the cellular contents and development of subsequent inflammation. T and B cells that have differentiated into memory cells are spared this fate.

Geriatrics Essentials

With aging, the immune system becomes less effective in the following ways:

- The immune system becomes less able to distinguish self from nonself, making autoimmune disorders more common.

- Macrophages destroy bacteria, cancer cells, and other Ag more slowly, possibly contributing to the increased incidence of cancer among the elderly.

- T cells respond less quickly to Ag.
- There are fewer lymphocytes that can respond to new Ag.
- The aging body produces less complement in response to bacterial infections.
- Less Ab is produced in response to Ag, and Ab is less able to attach to Ag, possibly contributing to the increased incidence of pneumonia, influenza, infectious endocarditis, and tetanus and the increased risk of death due to these disorders among the elderly. These changes may also partly explain why vaccines are less effective in the elderly.

Components of the Immune System

The immune system consists of cellular and molecular components that work together to destroy antigens (Ags).

Antigen-Presenting Cells

Although some Ags can stimulate the immune response directly, T cell-dependent acquired immune responses typically require antigen-presenting cells (APCs) to present Ag-derived peptides within major histocompatibility complex (MHC) molecules. Intracellular Ag (eg, viruses) can be processed and presented to CD8 cytotoxic T cells by any nucleated cell because all nucleated cells express class I MHC molecules. However, extracellular Ag must be processed into peptides and complexed with surface class II MHC molecules on professional APCs to be recognized by CD4 helper T (T_H) cells. The following cells constitutively express class II MHC molecules and therefore act as professional APCs:

- B cells
- Monocytes
- Macrophages
- Dendritic cells

Monocytes in the circulation are precursors to tissue macrophages. Monocytes migrate into tissues, where over about 8 h, they develop into macrophages under the influence of macrophage colony-stimulating factor (M-CSF), secreted by various cell types (eg, endothelial cells, fibroblasts). At infection sites, activated T cells secrete cytokines (eg, interferon-γ [IFN-γ]) that induce production of macrophage migration inhibitory factor, preventing macrophages from leaving.

Macrophages are activated by IFN-γ and granulocyte-macrophage colony-stimulating factor (GM-CSF). Activated macrophages kill intracellular organisms and secrete IL-1 and tumor necrosis factor-α (TNF-α). These cytokines potentiate the secretion of IFN-γ and GM-CSF and increase the expression of adhesion molecules on endothelial cells, facilitating leukocyte influx and destruction of pathogens.

Dendritic cells are present in the skin (as Langerhans' cells), lymph nodes, and tissues throughout the body. Dendritic cells in the skin act as sentinel APCs, taking up Ag, then travel to local lymph nodes where they can activate T cells. Follicular dendritic cells are a distinct lineage, do not express class II MHC molecules, and therefore do not present Ag to T_H cells. However, they have receptors for the crystallizable fragment (Fc) region of IgG and for complement, which enable them to bind with immune complexes and present the complex to B cells in germinal centers of secondary lymphoid organs.

Polymorphonuclear Leukocytes

Polymorphonuclear (PMN) leukocytes, also called granulocytes because their cytoplasm contains granules, include

- Neutrophils

• Eosinophils

• Basophils

• Mast cells

All, except for mast cells, occur in the circulation, and all have multilobed nuclei. Mast cells are tissue-based and functionally similar to circulating blood basophils.

Neutrophils constitute 40 to 70% of total WBCs; they are a first line of defense against infection. Mature neutrophils have a half-life of about 2 to 3 days. During acute inflammatory responses (eg, to infection), neutrophils, drawn by chemotactic factors and alerted by the expression of adhesion molecules on blood vessel endothelium, leave the circulation and enter tissues. Their purpose is to phagocytose and digest pathogens. Microorganisms are killed when phagocytosis generates lytic enzymes and reactive O_2 compounds (eg, superoxide, hypochlorous acid) and triggers release of granule contents (eg, defensins, proteases, bactericidal permeability-increasing protein, lactoferrin, and lysozymes). DNA and histones are also released, and they, with granule contents such as elastase, generate fibers in the surrounding tissues; the fibers may facilitate killing by trapping bacteria and focusing enzyme activity.

Eosinophils constitute up to 5% of WBCs. They target organisms too large to be engulfed; they kill by secreting toxic substances (eg, reactive O_2 compounds similar to those produced in neutrophils), major basic protein (which is toxic to parasites), eosinophil cationic protein, and several enzymes. Eosinophils are also a major source of inflammatory mediators (eg, prostaglandins, leukotrienes, platelet-activating factor, many cytokines).

Basophils constitute < 5% of WBCs and share several characteristics with mast cells, although the 2 cell types have distinct lineages. Both have high-affinity receptors for IgE called FcεRI. When these cells encounter certain Ags, the bivalent IgE molecules bound to the receptors become cross-linked, triggering cell degranulation with release of preformed inflammatory mediators (eg, histamine, platelet-activating factor) and generation of newly synthesized mediators (eg, leukotrienes, prostaglandins, thromboxanes).

Mast cells occur in different tissues of the body. Mucosal mast cell granules contain tryptase and chondroitin sulfate; connective tissue mast cell granules contain tryptase, chymase, and heparin. By releasing these mediators, mast cells play a key role in generating protective acute inflammatory responses; basophils and mast cells are the source of type I hypersensitivity reactions associated with atopic allergy (see p. 1113). Degranulation can be triggered by cross-linking of IgE receptors or by the anaphylatoxin complement fragments C3a and C5a.

Cytotoxic Leukocytes

Cytotoxic leukocytes include

• Natural killer cells

• Lymphokine-activated killers

Natural killer (NK) cells: Typical NK cells constitute 5 to 15% of peripheral blood mononuclear cells. They have a round nucleus and granular cytoplasm and induce apoptosis in infected or abnormal cells by a number of pathways. As cells of the innate response, they lack antigen-specific receptors and immunologic memory. NK cells are best characterized by $CD2^+$, $CD3^-$, $CD4^-$, $CD8^+$, $CD16^+$(a receptor for IgG-Fc), and $CD56^+$ surface markers.

Typical NK cells are thought to be important for tumor surveillance. NK cells express both activating and inhibitory receptors. The activating receptors on NK cells can recognize numerous ligands on target cells (eg, MHC class I-related chain A [MICA] and chain B [MICB]); the inhibitory receptors on NK cells recognize MHC class I molecules. NK cells can kill their target only when there is no strong signal from

inhibitory receptors. MHC class I molecules (normally expressed on nucleated cells) therefore prevent destruction of cells; their absence indicates that the cell is infected with certain viruses that inhibit MHC expression or has lost MHC expression because cancer has changed the cell.

NK cells can also secrete several cytokines (eg, IFN-γ, IL-1, TNF-α); they are a major source of IFN-γ. By secreting IFN-γ, NK cells can influence the acquired immune system by promoting differentiation of type 1 helper T (T_H1) cells and inhibiting that of type 2 (T_H2) cells.

Lymphokine-activated killers (LAK): Some leukocytes develop into potent lymphokine-activated killers, capable of killing a wide spectrum of tumor target cells and abnormal lymphocytes (eg, infected with certain viruses). These cells are a phenomenon rather than a unique subset of cells. LAK precursors are heterogeneous but can be classified primarily as NK-like (most common) or T-cell-like.

Lymphocytes

The 2 main types of lymphocytes are

• B cells (which mature in bone marrow)

• T cells (which mature in the thymus)

They are morphologically indistinguishable but have different immune functions. They can be distinguished by Ag-specific surface receptors and molecules called clusters of differentiation (CDs), whose presence and absence define some subsets. More than 300 CDs have been identified (for further information on CD Ags, see the Human Cell Differentiation Molecules web site at www.hlda8.org/). Each lymphocyte recognizes a specific Ag via surface receptors.

B cells: About 5 to 15% of lymphocytes in the blood are B cells; they are also present in the spleen, lymph nodes, and mucosa-associated lymphoid tissues. B cells can present Ag to T cells, but their primary function is to develop into plasma cells, which manufacture and secrete antibodies (Abs—see p. 1083).

After random rearrangement of the genes that encode immunoglobulin (Ig), B cells have the potential to recognize an almost limitless number of unique Ags. Gene rearrangement occurs in programmed steps in the bone marrow during B-cell development. The process starts with a committed stem cell, continues through pro-B and pre-B cell stages, and results in an immature B cell. If an immature B cell interacts with Ag, it may become inactivated (tolerant) or be eliminated (by apoptosis). Immature B cells that are not inactivated or eliminated may continue to develop into mature naive B cells, leave the marrow, and enter peripheral lymphoid organs, where they may encounter Ag. Their response to Ag has 2 stages:

- **Primary immune response:** When mature naive B cells first encounter Ag, they become lymphoblasts, undergo clonal proliferation, and differentiate into memory cells, which can respond to the same Ag in the future, or into mature Ab-secreting plasma cells. After first exposure, there is a latent period of days before Ab is produced. Then, only IgM is produced. After that, with the help of T cells, B cells can further rearrange their Ig genes and switch to production of IgG, IgA, or IgE. Thus, after first exposure, the response is slow and provides limited protective immunity.

- **Secondary (anamnestic or booster) immune response:** When memory B and T_H cells are reexposed to the Ag, the memory B cells rapidly proliferate, differentiate into mature plasma cells, and promptly produce large amounts of Ab (chiefly IgG because of a T cell-induced isotype switch). The Ab is released into the blood and other tissues, where it can react with Ag. Thus, after reexposure, the immune response is faster and more effective.

T cells: T cells develop from bone marrow stem cells that travel to the thymus, where they go through rigorous selection. There are 3 main types of T cell:

• Helper

• Regulatory

• Cytotoxic

In selection, T cells that react to self Ag presented by self MHC molecules or to self MHC molecules (regardless of the Ag presented) are eliminated by apoptosis. Only T cells that can recognize nonself Ag complexed to self MHC molecules survive; they leave the thymus for peripheral blood and lymphoid tissues.

Most mature T cells express either CD4 or CD8 and have an Ag-binding, Ig-like surface receptor called the T-cell receptor (TCR). Genes that encode the TCR, like Ig genes, are rearranged, resulting in defined specificity and affinity for the Ag peptide displayed in the MHC molecule of an APC. As for B cells, the number of T-cell specificities is almost limitless.

For T cells to be activated, the TCR must engage with Ag-MHC. Costimulatory accessory molecules must also interact; otherwise, the T cell becomes anergic or dies by apoptosis. Some accessory molecules (eg, CTLA-4) inhibit previously activated T cells and thus dampen the immune response.

Helper T (T_H) cells are usually CD4 but may be CD8. They differentiate from T_H0 cells into one of the following:

• T_H1 cells: In general, T_H1 cells promote cell-mediated immunity via cytotoxic T cells and macrophages.

• T_H2 cells: T_H2 cells promote Ab production by B cells (humoral immunity).

• T_H17 cells: T_H17 cells promote tissue inflammation.

Each cell type secretes several cytokines (see Table 125-1). Different patterns of cytokine production identify other T_H-cell functional phenotypes.

The distinction between the different T_H cells is clinically relevant. For example, a T_H1 response dominates in tuberculoid leprosy, and a T_H2 response dominates in lepromatous leprosy. A T_H1 response is characteristic of certain autoimmune disorders (eg, type 1 diabetes, multiple sclerosis), and a T_H2 response promotes IgE production and development of allergic disorders, as well as helps B cells produce autoantibodies in some autoimmune disorders (eg, Graves' disease, myasthenia gravis). T_H17 cells, via their role in inflammation, may also contribute to autoimmune disorders.

Regulatory T cells mediate suppression of immune responses. The process involves functional subsets of CD4 T cells that either secrete cytokines with immunosuppressive properties or suppress the immune response by poorly defined mechanisms that require cell-to-cell contact. Some regulatory T cells express the CD8 T-cell phenotype.

[**Table 125-1.** Functions of T Cells]

Cytotoxic T (T_C) cells are usually CD8 but may be CD4; they are vital for eliminating intracellular pathogens, especially viruses. T_C cells play a role in organ transplant rejection.

T_C-cell development involves 3 phases:

• A precursor cell that, when appropriately stimulated, can differentiate into a T_C cell

• An effector cell that has differentiated and can kill its appropriate target

• A memory cell that is quiescent (no longer stimulated) but is ready to become an effector when restimulated by the original Ag-MHC combination

Fully activated TC cells, like NK cells, can kill an infected target cell by inducing apoptosis.

T_C cells may be

- Syngeneic: Generated in response to self (autologous) cells modified by viral infection or other foreign proteins

- Allogeneic: Generated in response to cells that express foreign MHC products (eg, in organ transplantation when the donor's MHC molecules differ from the recipient's) Some T_C cells can directly recognize foreign MHC (direct pathway); others may recognize fragments of foreign MHC presented by self MHC molecules of the transplant recipient (indirect pathway).

NK T cells are a distinct subset of T cells. Activated NK T cells secrete IL-4 and IFN-γ and may help regulate immune responses.

Antibodies

Abs act as the Ag receptor on the surface of B cells and, in response to Ag, are subsequently secreted by plasma cells. Abs recognize specific configurations (epitopes, or antigenic determinants) on the surfaces of Ags (eg, proteins, polysaccharides, nucleic acids). Abs and Ags fit tightly together because their shape and other surface properties (eg, charge) are complementary. The same Ab molecule can cross-react with related Ags if their epitopes are similar enough to those of the original Ag.

Structure: Abs consist of 4 polypeptide chains (2 identical heavy chains and 2 identical light chains) joined by disulfide bonds to produce a Y configuration (see Fig. 125-1). The heavy and light chains are divided into a variable (V) region and a constant (C) region.

V regions are located at the amino-terminal ends of the Y arms; they are called variable because the amino acids they contain are different in different Abs. The amino acids present determine the specificity of the Ig. Hypervariable regions within the V regions contain idiotypic determinants, to which certain natural (anti-idiotype) Abs can bind; this binding may help regulate B-cell responses. A B cell can switch the Ig heavy chain isotype it produces, but it retains its heavy chain V region and the entire light-chain, thereby retaining antigenic specificity.

[**Fig. 125-1.** B-cell receptor.]

The **C region** contains a relatively constant sequence of amino acids that is distinctive for each Ig isotype.

The amino-terminal (variable) end of the Ab binds to Ag to form an Ab-Ag complex. The Ag-binding (Fab) portion of Ig consists of a light chain and a fragment of a heavy chain and contains the V region of the Ig molecule (ie, the combining sites). The crystallizable fragment (Fc) contains most of the C region of the heavy chains; Fc is responsible for complement activation and binds to Fc receptors on cells.

Antibody classes: Antibodies are divided into 5 classes:

- IgM

- IgG

- IgA

- IgD

- IgE

The classes are defined by their type of heavy chain (μ for IgM, γ for IgG, α for IgA, ε for IgE, and δ for IgD); there are also 2 types of light chains (κ and λ). Each of the 5 Ig classes can bear either κ or λ light

chains.

IgM is the first Ab formed after exposure to new Ag. It has 5 Y-shaped molecules (10 heavy chains and 10 light chains), linked by a single joining (J) chain. IgM circulates primarily in the intravascular space; it complexes with and agglutinates Ag and can activate complement, thereby facilitating phagocytosis. Isohemagglutinins and many Abs to gram-negative bacteria are IgM. Monomeric IgM acts as a surface Ag receptor on B cells.

IgG is the most prevalent Ig isotype in serum and is present also in intravascular and extravascular spaces. It coats Ag to activate complement and facilitate phagocytosis by neutrophils and macrophages. IgG is the primary circulating Ig produced after reexposure to Ag (secondary immune response) and is the predominant isotype contained in commercial γ-globulin products. IgG protects against bacteria, viruses, and toxins; it is the only Ig isotype that crosses the placenta.

There are 4 subclasses of IgG: IgG1, IgG2, IgG3, and IgG4. They are numbered in descending order of serum concentration. IgG subclasses differ functionally mainly in their ability to activate complement; IgG1 and IgG3 are most efficient, IgG2 is less efficient, and IgG4 is inefficient. IgG1 and IgG3 are efficient mediators of Ab-dependent cellular cytotoxicity; IgG4 and IgG2 are less so.

IgA occurs at mucosal surfaces, in serum, and in secretions (saliva; tears; respiratory, GU, and GI tract secretions; colostrum), where it provides an early antibacterial and antiviral defense. J chain links IgA into a dimer to form secretory IgA. Secretory IgA is synthesized by plasma cells in the subepithelial regions of the GI and respiratory tracts.

IgD is coexpressed with IgM on the surface of naive B cells. Whether these 2 classes function differently on the surface of the B cell and, if so, how differently are unclear. They may simply be an example of molecular degeneracy. Serum IgD levels are very low, and the function of circulating IgD is unknown.

IgE is present in low levels in serum and in respiratory and GI mucous secretions. IgE binds with high affinity to receptors present in high levels on mast cells and basophils and to a lesser extent on several other hematopoietic cells, including dendritic cells. If Ag bridges 2 IgE molecules bound to the mast cell or basophil surface, the cells degranulate, releasing chemical mediators that cause an inflammatory response. IgE levels are elevated in atopic disorders (eg, allergic or extrinsic asthma, hay fever, atopic dermatitis) and parasitic infections.

Acute Phase Reactants

Acute phase reactants are plasma proteins whose levels dramatically increase if infection or tissue damage occurs. Most dramatically increased are C-reactive protein and mannose-binding lectin (which fix complement and act as opsonins), the transport protein α_1-acid glycoprotein, and serum amyloid P component. Many acute phase reactants are made in the liver. Collectively, they may help limit tissue injury, enhance host resistance to infection, and promote tissue repair and resolution of inflammation.

Cytokines

Cytokines are polypeptides secreted by immune and other cells when the cell interacts with a specific Ag, endotoxin, or other cytokines. Main categories include

- IFNs (IFN-α, IFN-β, IFN-γ)
- TNFs (TNF-α, lymphotoxin-α, lymphotoxin-β)
- ILs
- Chemokines
- TGFs

• Hematopoietic colony-stimulating factors (CSFs)

Although lymphocyte interaction with a specific Ag triggers cytokine secretion, cytokines themselves are not Ag-specific; thus, they bridge innate and acquired immunity and generally influence the magnitude of inflammatory or immune responses. They act sequentially, synergistically, or antagonistically. They may act in an autocrine or paracrine manner.

Cytokines deliver their signals via cell surface receptors. For example, the IL-2 receptor consists of 3 chains: α, β, and γ. The receptor's affinity for IL-2 is high if all 3 chains are expressed, intermediate if only the β and γ chains are expressed, or low if only the α chain is expressed. Mutations or deletion of the γ chain is the basis for X-linked severe combined immunodeficiency (see p. 1106).

Chemokines induce chemotaxis and migration of leukocytes. There are 4 subsets, defined by the number of intervening amino acids between the first 2 cysteine residues in the molecule. Chemokine receptors (CCR5 on memory T cells, monocytes/macrophages, and dendritic cells; CXCR4 on resting T cells) act as core-ceptors for entry of HIV into cells.

Human Leukocyte Antigen System

The human leukocyte antigen (HLA) system, the major histocompatibility complex (MHC) in humans, is controlled by genes located on chromosome 6. It encodes cell surface molecules specialized to present antigenic peptides to the T-cell receptor (TCR) on T cells. MHC molecules that present antigen (Ag) are divided into 2 main classes.

Class I MHC molecules are present on the surface of all nucleated cells and platelets. These polypeptides consist of a heavy chain bound to a β_2-microglobulin molecule. The heavy chain consists of 2 peptide-binding domains, an Ig-like domain, and a transmembrane region with a cytoplasmic tail. The heavy chain of the class I molecule is encoded by genes at HLA-A, HLA-B, and HLA-C loci. Lymphocytes that express CD8 molecules react with class I MHC molecules. These lymphocytes often have a cytotoxic function, requiring them to be capable of recognizing any infected cell. All nucleated cells express class I MHC molecules and can thus act as antigen-presenting cells for CD8 T cells (CD8 binds to the nonpolymorphic part of the class I heavy chain). Some class I MHC genes encode nonclassical MHC molecules, such as HLA-G (which may play a role in protecting the fetus from the maternal immune response) and HLA-E (which presents peptides to certain receptors on natural killer cells).

Class II MHC molecules are usually present only on professional Ag-presenting cells (B cells, macrophages, dendritic cells, Langerhans' cells), thymic epithelium, and activated (but not resting) T cells; most nucleated cells can be induced to express class II MHC molecules by interferon (IFN)-γ. Class II MHC molecules consist of 2 polypeptide (α and β) chains; each chain has a peptide-binding domain, an Ig-like domain, and a transmembrane region with a cytoplasmic tail. Both polypeptide chains are encoded by genes in the HLA-DP, -DQ, or -DR region of chromosome 6. Lymphocytes reactive to class II molecules express CD4 and are often helper T cells.

The MHC class III region of the genome encodes several molecules important in inflammation; they include complement components C2, C4, and factor B; tumor necrosis factor (TNF)-α; lymphotoxin-α; lymphotoxin-β; and 3 heat shock proteins.

Individual alleles of the class I and II loci in the HLA system are given standard designations (eg, HLA-A1, -B5, -Cw1, -DR1). Alleles defined by DNA sequencing are named to identify the gene and to give each allele a unique number composed of the HLA locus, an asterisk, 2 numbers representing the serologic equivalent of the Ag, and 2 numbers representing the specific allele (eg, A*0201, DRB1*0103, DQA1*0102). Sometimes another number is added to identify a different subtype.

Some disorders are linked to specific HLA alleles (eg, psoriasis to HLA-Cw6, ankylosing spondylitis and reactive arthritis to HLA-B27, narcolepsy to HLA-DR2 and HLA-DQB1*0602, type 1 diabetes mellitus to HLA-DQ2 and HLA-DQ8, multiple sclerosis to HLA-DR2, RA to HLA-DRB1).

Complement System

The complement system is an enzyme cascade that helps defend against infection. Many complement proteins occur in serum as inactive enzyme precursors (zymogens); others reside on cell surfaces. The complement system bridges innate and acquired immunity by

• Augmenting antibody (Ab) responses and immunologic memory

• Lysing foreign cells

• Clearing immune complexes and apoptotic cells

Complement components have many biologic functions (eg, stimulation of chemotaxis, triggering of mast cell degranulation independent of IgE).

Complement activation: There are 3 pathways of complement activation (see Fig. 125-2):

• Classical

• Lectin

• Alternative

Classical pathway components are labeled with a C and a number (eg, C1, C3), based on the order in which they were identified. Alternative pathway components are often lettered (eg, factor B, factor D) or named (eg, properdin).

Classical pathway activation is Ab-dependent, occurring when C1 interacts with Ag-IgM or aggregated Ag-IgG complexes, or Ab-independent, occurring when polyanions (eg, heparin, protamine, DNA and RNA from apoptotic cells), gram-negative bacteria, or bound C-reactive protein reacts directly with C1. This pathway is regulated by C1 inhibitor (C1-INH). Hereditary angioedema is due to a genetic deficiency of C1-INH.

Lectin pathway activation is Ab-independent; it occurs when mannose-binding lectin (MBL), a serum protein, binds to mannose or fructose groups on bacterial cell walls, yeast walls, or viruses. This pathway otherwise resembles the classical pathway structurally and functionally.

Alternate pathway activation occurs when components of microbial cell surfaces (eg, yeast walls, bacterial cell wall lipopolysaccharide [endotoxin]) or Ig (eg, nephritic factor, aggregated IgA) cleave small amounts of C3. This pathway is regulated by properdin, factor H, and decay-accelerating factor.

The 3 activation pathways converge into a final common pathway when C3 convertase cleaves C3 into C3a and C3b (see Fig. 125-2). C3 cleavage may result in formation of the membrane attack complex (MAC), the cytotoxic component of the complement system. MAC causes lysis of foreign cells.

Biologic activities: Complement components have other immune functions that are mediated by complement receptors (CR) on various cells.

• CR1 (CD35) promotes phagocytosis and helps clear immune complexes.

• CR2 (CD21) regulates Ab production by B cells and is the Epstein-Barr virus receptor.

• CR3 (CD11b/CD18), CR4 (CD11c/CD18), and C1q receptors play a role in phagocytosis.

• C3a, C5a, and C4a (weakly) have anaphylatoxin activity: They cause mast cell degranulation, leading to increased vascular permeability and smooth muscle contraction.

[**Fig. 125-2.** Complement activation pathways.]

• C3b acts as an opsonin by coating microorganisms and thereby enhancing their phagocytosis.

• C3d enhances Ab production by B cells.

• C5a is a neutrophil chemoattractant; it regulates neutrophil and monocyte activities and may cause augmented adherence of cells, degranulation and release of intracellular enzymes from granulocytes, production of toxic oxygen metabolites, and initiation of other cellular metabolic events.

Immunotherapeutics

Immunotherapeutic agents use or modify immune mechanisms. Use of these agents is rapidly evolving; new classes, new agents, and new uses of current agents are certain to be developed. A number of different classes of immunotherapeutic agents have been developed (see Table 125-2):

• Monoclonal antibodies

• Fusion proteins

• Soluble cytokine receptors

• Recombinant cytokines

• Small-molecule mimetics

Monoclonal antibodies: Monoclonal antibodies (mAbs) are manufactured in vitro to recognize specific targeted Ags; they are used to treat solid and hematopoietic tumors and inflammatory disorders. The mAbs that are currently in clinical use include

• Murine

• Chimeric

• Humanized

Murine mAbs are produced by injecting a mouse with an Ag, harvesting its spleen to obtain plasma cells that are producing Ab specific to that Ag, fusing those cells with immortal mouse myeloma cells, growing these hybridoma cells (eg, in cell culture), and harvesting

[**Table 125-2.** Some Immunotherapeutic Agents in Clinical Use*]

the Ab. Although mouse antibodies are similar to human antibodies, clinical use of murine mAbs is limited because they induce human anti-mouse Ab production, can cause immune complex serum sickness (a type III hypersensitivity reaction), and are rapidly cleared. An exception is muromonab-CD3 (OKT3), which effectively prevents acute rejection of solid organ transplants; it is typically given only once or twice to a patient receiving other immunosuppressants (see p. 1128).

To minimize the problems due to use of pure mouse Ab, researchers have used recombinant DNA techniques to create monoclonal Abs that are part human and part mouse. Depending on the proportion of the Ab molecule that is human, the resultant product is termed chimeric or humanized. In both cases, the process usually begins as above with production of mouse hybridoma cells that make Ab to the desired Ag. Then the DNA for some or all of the variable portion of the mouse Ab is merged with DNA for human immunoglobulin. The resultant DNA is placed in a mammalian cell culture, which then expresses the resultant gene, producing the desired Ab. If the mouse gene for the whole variable region is spliced next to the human constant region, the product is termed "chimeric"; if only parts of the mouse gene for the binding portion of the variable region are used, the product, termed "humanized," is even more human.

Chimeric mAbs activate Ag-presenting cells (APCs) and T cells more effectively than murine mAbs but can still induce production of human anti-chimeric Ab.

Humanized mAbs against various antigens (Ags) have been approved for the treatment of colorectal and breast cancer, leukemia, allergy, autoimmune disease, transplant rejection, and respiratory syncytial virus infection.

Fusion proteins: These hybrid proteins are created by linking together the gene sequences encoding all or part of 2 different proteins to generate a chimeric polypeptide that incorporates desirable attributes from the parent molecules (eg, a cell targeting component combined with a cell toxin). The circulating half-life of therapeutic proteins can also often be improved by fusing them to another protein that naturally has a longer serum half-life (eg, the Fc region of IgG).

Soluble cytokine receptors: Soluble versions of cytokine receptors are used as therapeutic reagents. They can block the action of cytokines by binding with them before they attach to their normal cell surface receptor.

Etanercept, a fusion protein, consists of 2 identical chains from the receptor for CD120b tumor necrosis factor (TNF)-α. This agent thus blocks TNF-α and is used to treat RA refractory to other treatments, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis.

Soluble IL receptors (eg, those for IL-1, IL-2, IL-4, IL-5, and IL-6) are being developed for treatment of inflammatory and allergic disorders and cancer.

Recombinant cytokines: Colony-stimulating factors (CSF), such as erythropoietin, granulocyte CSF (G-CSF), and granulocyte-macrophage CSF (GM-CSF), are used in patients undergoing chemotherapy or transplantation for hematologic disorders and cancers (see Table 125-2). Interferon-α (IFN-α) and IFN-γ are used to treat cancer, immunodeficiency disorders, and viral infections; IFN-β is used to treat relapsing multiple sclerosis. Many other cytokines are being studied.

Anakinra, used to treat RA, is a recombinant, slightly modified form of the naturally occurring IL-1R antagonist; this drug attaches to the IL-1 receptor and thus prevents binding of IL-1, but unlike IL-1, it does not activate the receptor.

Cells expressing cytokine receptors can be targeted by modified versions of the relevant cytokine (eg, denileukin diftitox, which is a fusion protein containing sequences from IL-2 and from diphtheria toxin). Denileukin is used in cutaneous T-cell lymphoma to target the toxin to cells expressing the CD25 component of the IL-2 receptor.

Small-molecule mimetics: Small linear peptides, cyclicized peptides, and small organic molecules have been developed as agonists or antagonists for various applications. Screening libraries of peptides and organic compounds can identify potential mimetics (eg, agonists for receptors for erythropoietin, thrombopoietin, and G-CSF).

Chapter 126. Immunodeficiency Disorders

Introduction

Immunodeficiency disorders increase susceptibility to infection. They may be secondary or primary; secondary is more common.

Secondary immunodeficiencies: Causes include systemic disorders (eg, diabetes, undernutrition, HIV infection) and immunosuppressive treatments (eg, chemotherapy, radiation therapy—see Table 126-1). Secondary immunodeficiency also occurs among critically ill, older, or hospitalized patients. Prolonged serious illness may impair immune responses; impairment is often reversible if the underlying illness resolves.

Immunodeficiency can result from loss of serum proteins (particularly IgG and albumin) through the kidneys in nephrotic syndrome, through skin in severe burns or dermatitis, or through the GI tract in enteropathy. Enteropathy may also lead to lymphocyte loss, resulting in lymphopenia. These disorders can mimic Band T-cell defects. Treatment focuses on the underlying disorder; a diet high in medium-chain triglycerides may decrease loss of Igs and lymphocytes from the GI tract and be remarkably beneficial.

Primary immunodeficiencies: These disorders are genetically determined; they may occur alone or as part of a syndrome. More than 200 have been described, and heterogeneity within each disorder may be considerable. The molecular basis for about 80% is known.

[**Table 126-1.** Causes of Secondary Immunodeficiency]

[
Table 126-2. Some Drugs that Cause Immunosuppression]

Primary immunodeficiencies typically manifest during infancy and childhood as abnormally frequent (recurrent) or unusual infections. About 70% of patients are < 20 yr at onset; because transmission is often X-linked, 60% are male. Overall incidence of symptomatic disease is about 1/280 people.

Primary immunodeficiencies are classified by the main component of the immune system that is deficient, absent, or defective (see Table 126-3):

• B cells (or Ig)

• T cells

• Natural killer cells (very rare)

• Phagocytic cells

• Complement proteins

As more molecular defects are defined, classifying immunodeficiencies by their molecular defects will be more appropriate.

B-cell defects causing Ig and antibody deficiencies account for 50 to 60% of primary immunodeficiencies. Serum Ig and antibody titers decrease, predisposing to infections with encapsulated gram-positive bacteria. The most common B-cell disorder is selective IgA deficiency.

T-cell disorders account for about 5 to 10% of primary immunodeficiencies and predispose to infection by viruses, *Pneumocystis jirovecii*, fungi, other opportunistic organisms, and many common pathogens. T-cell disorders also cause Ig deficiencies because the B- and T-cell immune systems are interdependent. The most common T-cell disorders are DiGeorge syndrome, ZAP-70 deficiency, X-linked lymphoproliferative syndrome, and chronic mucocutaneous candidiasis (see p. 1102).

Combined B- and T-cell defects account for about 20% of primary immunodeficiencies. The most important form is severe combined immunodeficiency (SCID). In some forms of combined immunodeficiency (eg, purine nucleoside phosphorylase deficiency), Ig levels are normal or elevated, but because of inadequate T-cell function, antibody formation is impaired.

Natural killer cell defects are very rare and may predispose to viral infections and tumors.

Phagocytic cell defects account for 10 to 15% of primary immunodeficiencies; the ability of phagocytic cells (eg, monocytes, macrophages, granulocytes such as neutrophils and eosinophils) to kill pathogens is impaired. Cutaneous staphylococcal and gram-negative infections are characteristic. The most common phagocytic cell defects are chronic granulomatous disease, leukocyte adhesion deficiency, and Chediak-Higashi syndrome.

Complement deficiencies are rare (≤ 2%); they include isolated deficiencies of complement components or inhibitors and may be hereditary or acquired. Hereditary deficiencies are autosomal recessive except for deficiencies of C1 inhibitor, which is autosomal dominant, and properdin, which is X-linked. The deficiencies result in defective opsonization, phagocytosis, and lysis of pathogens and in defective clearance of antigen-antibody complexes. Recurrent infection, due to defective opsonization, and autoimmune disorders (eg, SLE, glomerulonephritis), due to defective clearance of antigen-antibody complexes (see Table 126-3), are the most serious consequences. One of these deficiencies causes hereditary angioedema.

Primary immunodeficiency syndromes are genetically determined immunodeficiencies with immune and nonimmune defects. Nonimmune manifestations are often more easily recognized than those of the immunodeficiency. Examples are ataxia-telangiectasia, cartilage-hair hypoplasia, DiGeorge syndrome, hyper-IgE syndrome, and Wiskott-Aldrich syndrome.

Geriatrics Essentials

Some decrease in immunity occurs with aging. For example, in the elderly, the thymus

[**Table 126-3.** Primary Immunodeficiency Disorders]

tends to produce fewer naive T cells; thus, fewer T cells are available to respond to new antigens. The number of T cells does not decrease (because of oligoclonality), but these cells can recognize only a limited number of antigens.

Signal transduction (transmission of antigen-binding signal across the cell membrane into the cell) is impaired, making T cells less likely to respond to antigens. Also, helper T cells may be less likely to signal B cells to produce antibodies.

The number of neutrophils does not decrease, but these cells become less effective in phagocytosis and microbicidal action.

Undernutrition, common among the elderly, impairs immune responses. Ca, zinc, and vitamin E are particularly important to immunity. Risk of Ca deficiency is increased in the elderly, partly because with aging, the intestine becomes less able to absorb Ca. Also, the elderly may not ingest enough Ca in their diet. Zinc deficiency is very common among the institutionalized elderly and homebound patients.

Approach to the Patient With Suspected Immunodeficiency

Immunodeficiency typically manifests as recurrent infections. However, more likely causes of recurrent infections in children are repeated exposures to infection at day care or school (infants and children may normally have up to 10 respiratory infections/yr), and more likely causes in children and adults are inadequate duration of antibiotic treatment, resistant organisms, and other disorders that predispose to infection (eg, congenital heart defects, allergic rhinitis, ureteral or urethral stenosis, immotile cilia syndrome, asthma, cystic fibrosis, severe dermatitis).

Immunodeficiency should be suspected when recurrent infections are the following:

• Severe

• Complicated

• In multiple locations

• Resistant to treatment

• Caused by unusual organisms

Initially, infections due to immunodeficiency are typically upper and lower respiratory tract infections (eg, sinusitis, bronchitis, pneumonia) and gastroenteritis, but they may be serious bacterial infections (eg, meningitis, sepsis).

Immunodeficiency should also be suspected in infants or young children with chronic diarrhea and failure to thrive, especially when the diarrhea is caused by unusual viruses (eg, adenovirus) or fungi (eg, *Cryptosporidium* sp). Other signs include skin lesions (eg, eczema, warts, abscesses, pyoderma, alopecia), oral or esophageal thrush, oral ulcers, and periodontitis.

Less common manifestations include severe viral infection with herpes simplex or varicella zoster virus and CNS problems (eg, chronic encephalitis, delayed development, seizure disorder). Frequent use of antibiotics may mask many of the common symptoms and signs. Immunodeficiency should be considered particularly in patients with infections and an autoimmune disorder (eg, hemolytic anemia, thrombocytopenia).

Evaluation

History and physical examination are helpful but must be supplemented by immune function testing. Prenatal testing is available for many disorders and is indicated if there is a family history of immunodeficiency and the mutation has been identified in family members.

History: Clinicians should determine whether patients have a history of risk factors for infection or of symptoms and risk factors for secondary immunodeficiency disorders. Family history is very important.

Age when recurrent infections began is important. Onset of infections before age 12 mo suggests combined B- and T-cell defects or a B-cell defect, which becomes evident when maternal antibodies are disappearing (at about age 6 mo). In general, the earlier the age at onset in children, the more severe the immunodeficiency. Often, certain other primary immunodeficiencies (eg, common variable immunodeficiency [CVID]) do not manifest until adulthood.

Certain infections suggest certain immunodeficiency disorders (see Table 126-4); however, no infection is specific to any one disorder, and certain common infections (eg, respiratory viral or bacterial infections) occur in many.

Physical examination: Patients with immunodeficiency may or may not appear chronically ill. Macular rashes, vesicles, pyoderma, eczema, petechiae, alopecia, or telangiectasia may be evident.

Cervical lymph nodes and adenoid and tonsillar tissue are typically very small or absent in X-linked agammaglobulinemia, X-linked hyper-IgM syndrome, severe combined immunodeficiency (SCID), and other T-cell immunodeficiencies despite a history of recurrent infections. In certain other immunodeficiencies (eg, chronic granulomatous disease), lymph nodes of the head and neck may be enlarged and suppurative.

Tympanic membranes may be scarred or perforated. The nostrils may be crusted, indicating purulent nasal discharge. Chronic cough is common, as are lung crackles, especially in adults with CVID. The liver

and spleen are often enlarged in patients with CVID or chronic granulomatous disease. Muscle mass and fat deposits of the buttocks are decreased. In infants, skin around the anus may break down because of chronic diarrhea. Neurologic examination may detect delayed developmental milestones or ataxia.

Other characteristic findings tentatively suggest a clinical diagnosis (see Table 126-5).

Initial testing: If a specific secondary immunodeficiency disorder is suspected clinically, testing should focus on that disorder (eg, diabetes, HIV infection, cystic fibrosis, primary ciliary dyskinesia).

Tests are needed to confirm a diagnosis of immunodeficiency (see Table 126-6). Initial screening tests should include

• CBC with manual differential

• Quantitative Ig measurements

• Antibody titers

• Skin testing for delayed hypersensitivity

[**Table 126-4.** Some Clues in Patient History to Type of Immunodeficiency]

If results are normal, immunodeficiency (especially Ig deficiency) can be excluded. If results are abnormal, further tests in specialized laboratories are needed to identify specific deficiencies. If chronic infections are objectively documented, initial and specific tests may be done simultaneously.

CBC can detect abnormalities in one or more cell types (eg, WBCs, platelets) characteristic of specific disorders. However, many abnormalities are transient manifestations of infection, drug use, or other factors; thus, abnormalities should be confirmed and followed.

• **Neutropenia** (absolute neutrophil count < 1200 cells/μL) may be congenital or cyclic or may occur in aplastic anemia.

• **Lymphopenia** (lymphocytes < 2000/μL at birth, < 4500/μL at age 9 mo, or < 1000/μL in older children or adults) suggests a T-cell disorder because 70% of circulating lymphocytes are T cells.

• **Leukocytosis** that persists between infections may occur in leukocyte adhesion deficiency.

• **Thrombocytopenia** in male infants suggests Wiskott-Aldrich syndrome.

• **Anemia** may suggest anemia of chronic disease or autoimmune hemolytic anemia, which may occur in CVID and other immunodeficiencies.

Peripheral blood smear should be examined for Howell-Jolly bodies and other unusual RBC forms, which suggest primary asplenia or impaired splenic function. Granulocytes may have morphologic abnormalities (eg, giant granules in Chediak-Higashi syndrome).

Quantitative serum Ig levels are measured. Low serum levels of IgG, IgM, or IgA suggest antibody deficiency, but results must be compared with those of age-matched controls. An IgG level < 200 mg/dL usually indicates significant antibody deficiency, although such levels may occur in protein-losing enteropathies or nephrotic syndrome.

• **IgM antibodies** can be assessed by measuring isohemagglutinin titers (anti-A, anti-B). All patients except infants < 6 mo and people with blood type AB have natural antibodies at

[**Table 126-5.** Characteristic Clinical Findings in Some Primary Immunodeficiency Disorders]

a titer of ≥ 1:8 (anti-A) or ≥ 1:4 (anti-B). Antibodies to blood groups A and B and to some bacterial polysaccharides are selectively deficient in certain disorders (eg, Wiskott-Aldrich syndrome, complete IgG2 deficiency).

- **IgG antibody** titers can be assessed in immunized patients by measuring antibody titers before and after administration of vaccine antigens (*Haemophilus influenzae* type B, tetanus, diphtheria, conjugated or nonconjugated pneumococcal, and meningococcal antigens); a less-than-twofold increase in titer at 2 to 3 wk suggests antibody deficiency regardless of Ig levels. Natural antibodies (eg, antistreptolysin O, heterophil antibodies) may also be measured.

[**Table 126-6.** Initial and Additional Laboratory Tests for Immunodeficiency]

With **skin testing,** most immunocompetent adults, infants, and children react to 0.1 mL of *Candida albicans* extract (1:100 for infants and 1:1000 for older children and adults) injected intradermally. Positive reactivity, defined as erythema and induration > 5 mm at 24, 48, and 72 h, excludes a T-cell disorder. Lack of response does not confirm immunodeficiency in patients with no previous exposure to *Candida*.

Chest x-ray may be useful in some infants; an absent thymic shadow suggests a T-cell disorder, especially if the x-ray is obtained before onset of infection or other stresses that may shrink the thymus. Lateral pharyngeal x-ray may show absence of adenoidal tissue.

Additional testing: If clinical findings or initial tests suggest a specific disorder of immune cell or complement function, other tests are indicated.

If patients have recurrent infections and lymphopenia, lymphocyte phenotyping using flow cytometry and monoclonal antibodies to T, B, and natural killer (NK) cells is indicated to check for lymphocyte deficiency. If T cells are low or absent, invitro mitogen stimulation studies are done to assess T-cell function. If MHC antigen deficiency is suspected, serologic (not molecular) HLA typing is indicated.

If phagocytic cell defects are suspected, a flow cytometric respiratory burst assay can detect whether O_2 radicals are produced during phagocytosis; no production is characteristic of chronic granulomatous disease.

If the type or pattern of infections suggests complement deficiency, the serum dilution required to lyse 50% of antibody-coated RBCs (CH50) is measured. This test detects complement component deficiencies in the classical or alternative complement activation pathway but does not indicate which component is abnormal.

If examination or screening tests detect abnormalities suggesting lymphocyte or phagocytic cell defects, other tests can more precisely characterize specific disorders (see Table 126-7).

Prenatal diagnosis: An increasing number of primary immunodeficiency disorders can be diagnosed prenatally using chorionic villus sampling, cultured amniotic cells, or fetal blood sampling, but these tests are used only when a mutation in family members has already been identified (see p. 2602). X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, ataxia-telangiectasia, X-linked lymphoproliferative syndrome, all forms of SCID, and all forms of chronic granulomatous disease can be detected. Sex determination by ultrasonography can be used to exclude X-linked disorders.

Prognosis

Prognosis depends on the primary immunodeficiency disorder. Most patients with an Ig or a complement deficiency have a good prognosis with a near-normal life expectancy if they are diagnosed early, are treated appropriately, and have no coexisting chronic disorders (eg, pulmonary disorders such as bronchiectasis). Other immunodeficient patients (eg, those with a phagocytic cell defect or combined immunodeficiencies, such as Wiskott-Aldrich syndrome or ataxia-telangiectasia) have a guarded prognosis; most require intensive and frequent treatment. Some immunodeficient patients (eg, those with SCID) die during

[Table 126-7. Advanced Laboratory Tests for Immunodeficiency]

infancy unless immunity is provided through transplantation. All forms of SCID could be diagnosed at birth if a WBC count and manual differential of cord or peripheral blood were routinely done in neonates. Suspicion for SCID, a true pediatric emergency, must be high because prompt diagnosis is essential for survival. If done before patients reach age 3 mo, transplantation of bone marrow or stem cells from a matched or half-matched (haploidentical) relative is lifesaving in 95%.

Treatment

• Vaccines and avoidance of exposure to infection

• Antibiotics and sometimes surgery

• Replacement of missing immune components

Treatment generally involves preventing infection, managing acute infection, and replacing missing immune components when possible.

Infection prevention: Infection can be prevented by advising patients to avoid environmental exposures and giving live-virus vaccines (varicella, rotavirus, measles, mumps, rubella). Patients at risk of serious infections (eg, those with SCID, chronic granulomatous disease, Wiskott-Aldrich syndrome, or asplenia) or a specific infection (eg, with *Pneumocystis jirovecii* in patients with T-cell disorders) can be given prophylactic antibiotics (eg, 5 mg/kg trimethoprim/sulfamethoxazole po bid).

To prevent graft-vs-host disease after transfusions, clinicians should use blood products from cytomegalovirus-negative donors; the products should be filtered to remove WBCs and irradiated (15 to 30 Gy).

Management of acute infection: After appropriate cultures are obtained, antibiotics that target likely causes should be given promptly. Sometimes surgery (eg, to drain abscesses) is needed. Usually, self-limited viral infections cause severe persistent disease in immunocompromised patients. Antivirals (eg, amantadine, rimantadine, oseltamivir, or zanamivir for influenza; acyclovir for herpes simplex and varicella-zoster infections; ribavirin for respiratory syncytial virus or parainfluenza 3 infections) may be lifesaving.

Replacement of missing immune components: Such replacement helps prevent infection. Therapies used in more than one primary immunodeficiency disorder include the following:

• **IV immune globulin** (IVIG) is effective replacement therapy in most forms of antibody deficiency. The usual dose is 400 mg/kg once/mo; treatment is begun at a low infusion rate. Some patients need higher or more frequent doses. IVIG 800 mg/kg once/mo helps some antibody-deficient patients who do not respond well to conventional doses, particularly those with a chronic lung disorder. High-dose IVIG aims to keep IgG trough levels in the normal range (> 500 mg/dL). IVIG may also be given by slow sc infusions at weekly intervals.

• **Hematopoietic stem cell transplantation** using bone marrow, cord blood, or adult peripheral blood stem cells is effective for lethal T-cell and other immunodeficiencies. Pretransplantation chemotherapy is unnecessary in patients without T cells (eg, those with SCID). However, patients with intact T-cell function or partial T-cell deficiencies (eg, Wiskott-Aldrich syndrome, combined immunodeficiency with inadequate but not absent T-cell function) require pretransplantation chemotherapy to ensure graft acceptance. When a matched sibling donor is unavailable, haploidentical bone marrow from a parent can be used. In such cases, mature T cells that cause graft-vs-host disease must be rigorously depleted from parental marrow before it is given. Umbilical cord blood from an HLA-matched sibling can also be used as a source of stem cells. In some cases, bone marrow or umbilical cord blood from a matched unrelated donor can be used, but after transplantation, immunosuppressants are required to prevent graft-vs-host disease, and their use delays restoration of immunity.

Retroviral vector gene therapy has been successful in a few patients with X-linked and ADA-deficient SCID, but this treatment is not widely used because some patients with X-linked SCID developed leukemia.

Ataxia-Telangiectasia

Ataxia-telangiectasia results from a T-cell defect and causes progressive cerebellar ataxia, oculocutaneous telangiectasias, and recurrent sinopulmonary infections.

Inheritance is autosomal-recessive. Ataxia-telangiectasia is caused by mutations in the gene that encodes ataxia-telangiectasia-mutated (ATM) protein. ATM protein may be important in mitogenic signal transduction, meiotic recombination, and cell cycle control.

Age at onset of neurologic symptoms and evidence of immunodeficiency vary. Ataxia usually develops when children begin to walk. Progression of neurologic symptoms leads to severe disability. Speech becomes slurred, choreoathetoid movements and nystagmus develop, and muscle weakness usually progresses to muscle atrophy. Telangiectasias may not appear until age 4 to 6 yr; they are most prominent on the bulbar conjunctivae, ears, antecubital and popliteal fossae, and sides of the neck. Recurrent sinopulmonary infections lead to recurrent pneumonia, bronchiectasis, and chronic restrictive pulmonary disease. Patients often lack IgA and IgE and have a progressive T-cell defect. Certain endocrine abnormalities (eg, gonadal dysgenesis, testicular atrophy, diabetes mellitus) may occur.

Frequency of cancer (especially leukemia, brain tumors, and gastric cancer) is high, and frequency of chromosome breaks, consistent with a defect in DNA repair, is increased. Serum α_1-fetoprotein is usually elevated.

Diagnosis

Clinical findings of cerebellar ataxia (particularly when telangiectasias are present), low levels of IgA, and high levels of serumα_1-fetoprotein suggest the diagnosis. Diagnosis is confirmed by identifying mutations on both alleles of the gene for ATM protein.

Treatment

Treatment with antibiotics or IV immune globulin may help, but no treatment is effective for the CNS abnormalities. Thus, neurologic deterioration progresses, causing death, usually by age 30.

Chediak-Higashi Syndrome

Chediak-Higashi syndrome is characterized by impaired lysis of phagocytized bacteria, resulting in recurrent bacterial respiratory and other infections and oculocutaneous albinism.

Chediak-Higashi syndrome is rare. Inheritance is autosomal recessive. The syndrome is caused by a mutation in a gene that regulates intracellular protein trafficking. Giant lysosomal granules develop in neutrophils and other cells (eg, melanocytes, neural Schwann cells). The abnormal lysosomes cannot fuse with phagosomes, so ingested bacteria cannot be lysed normally.

Clinical findings include oculocutaneous albinism and susceptibility to recurrent respiratory and other infections. In about 85% of patients, an accelerated phase occurs, causing fever, jaundice, hepatosplenomegaly, lymphadenopathy, pancytopenia, bleeding diathesis, and neurologic changes. Once the accelerated phase occurs, the syndrome is usually fatal within 30 mo.

A peripheral blood smear is examined for giant granules in neutrophils and other cells; a bone marrow smear is examined for giant inclusion bodies in leukocyte precursor cells.

Transplantation of unfractionated HLA-identical bone marrow after pretransplantation cytoreductive chemotherapy may be curative.

Chronic Granulomatous Disease

Chronic granulomatous disease is characterized by WBCs that cannot produce activated O_2 compounds and by defects in phagocytic cell microbicidal function. Manifestations include recurrent infections; multiple granulomatous lesions of the lungs, liver, lymph nodes, and GI and GU tract; abscesses; lymphadenitis; hypergammaglobulinemia; elevated ESR; and anemia. Diagnosis is by assessing O_2 radical production in WBCs via a flow cytometric respiratory burst assay. Treatment is with antibiotics, antifungal drugs, and interferon-γ; granulocyte transfusions may be needed.

More than 50% of cases of chronic granulomatous disease (CGD) are inherited as an X-linked recessive trait and thus occur only in males; in the rest, inheritance is autosomal recessive. In CGD, WBCs do not produce hydrogen peroxide, superoxide, and other activated O_2 compounds because nicotinamide adenine dinucleotide phosphate oxidase activity is deficient. Phagocytic cell microbicidal function is defective; thus, bacteria and fungi are not killed despite normal phagocytosis.

Symptoms and Signs

CGD usually begins with recurrent abscesses during early childhood, but in a few patients, onset is delayed until the early teens. Typical pathogens are catalase-producing organisms (eg, *Staphylococcus aureus*; *Escherichia coli*; *Serratia, Klebsiella*, and *Pseudomonas* sp; fungi). *Aspergillus* infections are the leading cause of death.

Multiple granulomatous lesions occur in the lungs, liver, lymph nodes, and GI and GU tract (causing obstruction). Suppurative lymphadenitis, hepatosplenomegaly, pneumonia, and hematologic evidence of chronic infection are common. Skin, lymph node, lung, liver, and perianal abscesses; stomatitis; and osteomyelitis also occur. Growth may be delayed.

Diagnosis

Diagnosis is by a flow cytometric respiratory burst assay to detect O_2 radical production. The test can also identify female carriers of the X-linked form. Hypergammaglobulinemia and anemia can occur; ESR is elevated.

Treatment

• Prophylactic antibiotics, sometimes including antifungals

• Sometimes interferon (IFN)-γ

• For severe infections, granulocyte transfusions or bone marrow transplantation

Treatment is continuous prophylactic antibiotics, particularly trimethoprim/sulfamethoxazole 160/800 mg po bid alone or with cephalexin 500 mg po q 8 h. Oral antifungals are given as primary prophylaxis or are added if fungal infections occur even once; most useful are itraconazole po q 12 h (100 mg for patients < 13 yr; 200 mg for those ≥ 13 yr or weighing > 50 kg), voriconazole po q 12 h (100 mg for those weighing < 40 kg; 200 mg for those weighing ≥ 40 kg), or posaconazole (400 mg bid). IFN-γ may reduce severity and frequency of infections. Usual dose is 50 $\mu g/m^2$ sc 3 times/wk.

Granulocyte transfusions can be lifesaving when infections are severe. When preceded by pretransplantation chemotherapy, HLA-identical sibling bone marrow transplantation may be successful.

Chronic Mucocutaneous Candidiasis

Chronic mucocutaneous candidiasis is persistent or recurrent candidal infection due to T-cell defects.

Inheritance is autosomal dominant or recessive. Patients have cutaneous anergy to *Candida*, absent proliferative responses to *Candida* antigen (but normal proliferative responses to mitogens), and intact antibody response to *Candida* and other antigens. Candidiasis recurs or persists, usually beginning during infancy but sometimes during early adulthood. Life span is not affected.

Patients with the recessive form (autoimmune polyendocrinopathy-candidosis-ectodermal dystrophy) develop endocrine disorders (eg, hypoparathyroidism, adrenal insufficiency, hypogonadism, thyroid disease, diabetes), and hepatitis.

Thrush is common, as are infections of the scalp, skin, nails, and GI and vaginal mucosa. Severity varies. Nails may be thickened, cracked, and discolored, with edema and erythema of the surrounding periungual tissue, resembling clubbing. Skin lesions are crusted, pustular, erythematous, and hyperkeratotic. Scalp lesions may result in scarring alopecia. Infants often present with refractory thrush, candidal diaper dermatitis, or both.

Diagnosis

Diagnosis is based on the presence of recurrent candidal skin or mucosal lesions when no other known causes of candidal infection (eg, diabetes, antibiotic use) are present. Candidal lesions are confirmed by other tests (eg, potassium hydroxide wet mount of scrapings).

Treatment

• Antifungal drugs

Usually, the infections can be controlled with a topical antifungal. However, long-term treatment with a systemic antifungal drug (eg, amphotericin B, fluconazole, ketoconazole) may be needed. Topical antifungals are usually ineffective. Sometimes an immunomodulator (eg, transfer factor) is also used.

Common Variable Immunodeficiency

Common variable immunodeficiency (acquired or adult-onset hypogammaglobulinemia) is characterized by low immunoglobulin (Ig) levels with phenotypically normal B cells that can proliferate but do not develop into Ig-producing cells.

Common variable immunodeficiency (CVID) includes several different molecular defects, but in most patients, the molecular defect is unknown. CVID is clinically similar to X-linked agammaglobulinemia in the types of infections that develop, but onset tends to be later, even in adulthood. T-cell immunity may be impaired in some patients. Autoimmune disorders (eg, SLE, Addison's disease, thyroiditis, RA, alopecia areata, autoimmune thrombocytopenia, autoimmune hemolytic or pernicious anemia) can occur, as can malabsorption, nodular lymphoid hyperplasia of the GI tract, lymphoid interstitial pneumonia, splenomegaly, and bronchiectasis. Gastric carcinoma and lymphoma occur in 10% of patients.

Diagnosis

• Measurement of serum Ig and antibody titers

• Flow cytometry

• Serum protein electrophoresis

Diagnosis is suggested by familial clustering of autoimmune disorders and is confirmed by measuring serum Ig and antibody titers to protein and polysaccharide vaccine antigens. If either measurement is low, B-cell quantification by flow cytometry is indicated to distinguish CVID from X-linked agammaglobulinemia, multiple myeloma, and chronic lymphocytic leukemia. Serum protein electrophoresis is indicated to screen for monoclonal gammopathies (eg, myeloma), which may be associated with reduced levels of other Ig isotypes. If patients are treated with IV immune globulin (IVIG) before testing, serologic tests have no

value because the antibodies are from the IVIG.

Treatment

Treatment consists of IVIG 400 mg/kg once/mo and antibiotics as needed to treat infection. Rituximab or a corticosteroid may be required to treat autoimmune disorders.

DiGeorge Syndrome

DiGeorge syndrome is thymic and parathyroid hypoplasia or aplasia leading to T-cell immunodeficiency and hypoparathyroidism.

DiGeorge syndrome results from gene deletions in the DiGeorge chromosomal region at 22q11, mutations in genes at chromosome 10p13, and mutations in other unknown genes, which cause dysembryogenesis of structures that develop from pharyngeal pouches during the 8th wk of gestation. Most cases are sporadic; boys and girls are equally affected. Di-George syndrome may be partial (some T-cell function exists) or complete (T-cell function is absent).

Infants have low-set ears, midline facial clefts, a small receding mandible, hypertelorism, a shortened philtrum, and a congenital heart disorder. They also have thymic and parathyroid hypoplasia or aplasia, causing T-cell deficiency and hypoparathyroidism. Recurrent infections begin soon after birth, but the degree of immunodeficiency varies considerably, and T-cell function may improve spontaneously. Hypocalcemic tetany appears within 24 to 48 h of birth.

Prognosis often depends on severity of the heart disorder.

Diagnosis

• Immune function assessment

• Parathyroid function assessment

• Chromosome analysis

Diagnosis is based on clinical findings. An absolute lymphocyte count is done, followed by B- and T-cell counts if leukopenia is detected; blood tests to evaluate T-cell and parathyroid function are done. A lateral chest x-ray may help evaluate thymic shadow. Fluorescent in situ hybridization (FISH) testing can detect the chromosomal deletion in the 22q11 region; standard chromosomal tests to check for other abnormalities may also be done. Cardiac catheterization may be needed to identify heart defects.

Treatment

In partial DiGeorge syndrome, hypoparathyroidism is treated with Ca and vitamin D supplementation; long-term survival is not affected. Complete DiGeorge syndrome is fatal without treatment, which is transplantation of cultured thymus tissue.

Hyper-IgE Syndrome

Hyper-IgE (Buckley) syndrome is combined Band T-cell immunodeficiency characterized by recurrent staphylococcal abscesses of the skin, lungs, joints, and viscera.

Inheritance is autosomal dominant with incomplete penetrance; it is caused by mutations in the *STAT3* (signal transducer and activator of transcription 3) gene.

Hyper-IgE syndrome starts during infancy. It typically causes recurrent staphylococcal abscesses of the skin, lungs, joints, and viscera with pulmonary pneumatoceles and a pruritic eosinophilic dermatitis. Patients have coarse facial features, delayed shedding of baby teeth, osteopenia, and recurrent fractures. All have tissue and blood eosinophilia and very high IgE levels (> 1000 IU/mL [> 2400 µg/L]).

Diagnosis is suspected based on symptoms and confirmed by measurement of serum IgE levels. Genetic testing can identify the abnormal gene.

Treatment consists of lifelong continuous antistaphylococcal antibiotics (eg, dicloxacillin, cephalexin).

Hyper-IgM Syndrome

Hyper-IgM syndrome is an Ig deficiency characterized by normal or elevated serum IgM levels and decreased levels or absence of other serum Igs, resulting in susceptibility to bacterial infections.

Hyper-IgM syndrome may be X-linked or autosomal. Most cases are caused by mutations in a gene that is located on the X chromosome; this gene encodes a protein (CD154, or CD40 ligand) on the surfaces of activated helper T cells. In the presence of cytokines, normal CD40 ligand interacts with B cells and thus signals them to switch from producing IgM to producing IgA, IgG, or IgE.

In X-linked hyper-IgM syndrome, T cells lack functional CD40 ligand and cannot signal B cells to switch. Thus, B cells produce only IgM; IgM levels may be normal or elevated. Patients with this form may have severe neutropenia and often present during infancy with *Pneumocystis jirovecii* pneumonia. Otherwise, clinical presentation is similar to that of X-linked agammaglobulinemia and includes recurrent pyogenic bacterial sinopulmonary infections during the first 2 yr of life. Susceptibility to *Cryptosporidium* infections may be increased. Lymphoid tissue is very small because germinal centers are missing. Many patients die before puberty, and those who live longer often develop cirrhosis or B-cell lymphomas.

At least 4 autosomal recessive forms involve a B-cell defect. In 2 of these forms (deficiency of activation-induced cytidine deaminase or uracil DNA glycosylase [UNG]), serum IgM levels are much higher than in the X-linked form; lymphoid hyperplasia (including lymphadenopathy, splenomegaly, and tonsillar hypertrophy) is present, and autoimmune disorders may be present.

Diagnosis

Diagnosis is clinical and by detecting normal or elevated serum IgM levels and low levels or absence of other Igs.

Treatment

Treatment is IV immune globulin 400 mg/kg once/mo. For the X-linked form, granulocyte colony-stimulating factor is also given as needed for neutropenia, and because prognosis is poor, bone marrow transplantation is preferred if an HLA-identical sibling donor is available.

IgA Deficiency

IgA deficiency is an IgA level < 10 mg/dL with normal IgG and IgM levels. It is the most common primary immunodeficiency. Many patients are asymptomatic, but some develop recurrent infections and autoimmune disorders. Some patients develop common variable immunodeficiency, and some remit spontaneously. Diagnosis is by measuring serum Igs. Treatment is avoidance of blood products that contain IgA; antibiotics are given as needed.

IgA deficiency affects up to 1/333 people. Transmission is autosomal dominant with incomplete penetrance. IgA deficiency is commonly associated with certain HLA haplotypes, and rare alleles or deletions of genes in the major histocompatibility complex (MHC) class III region (see p. 1085) are common. IgA deficiency also occurs in siblings of children with common variable immunodeficiency (CVID) and evolves into CVID in some patients. Use of drugs such as phenytoin, sulfasalazine, colloidal gold and D-penicillamine may lead to IgA deficiency in genetically susceptible patients.

Symptoms and Signs

Many patients are asymptomatic; others have recurrent sinopulmonary infections, diarrhea, allergies, or autoimmune disorders (eg, celiac or inflammatory bowel disease, SLE, chronic active hepatitis). Anti-IgA antibodies may develop after exposure to IgA in transfusions; anaphylactic reactions to IV immune globulin (IVIG) and other blood products that contain IgA may occur.

Diagnosis

• Clinical evaluation

• Measurement of serum Ig levels and antibody titers

Diagnosis is suspected in patients who have recurrent infections (including giardiasis); anaphylactic transfusion reactions; or a family history of CVID, IgA deficiency, or autoimmune disorders or who are taking drugs that lead to IgA deficiency. Diagnosis is confirmed by a serum IgA level < 10 mg/dL with normal IgG and IgM levels and normal antibody titers in response to vaccine antigens.

Prognosis

A few IgA-deficient patients develop CVID over time; others improve spontaneously. Prognosis is worse if an autoimmune disorder develops.

Treatment

• Avoidance of blood products that contain IgA

• Antibiotics as needed

Treatment is avoidance of blood products that contain IgA because even trace amounts can elicit an anti-IgA-mediated anaphylactic reaction. If RBC transfusion is needed, only washed RBCs or frozen blood can be used.

Antibiotics are given as needed for bacterial infections of the ears, sinuses, lungs, or GI or GU tract.

IVIG is contraindicated because many patients have antibodies to IgA and because IVIG is > 99% IgG, which patients do not need. Patients are advised to wear an identification bracelet to prevent inadvertent plasma or IVIG administration, which could lead to anaphylaxis.

Leukocyte Adhesion Deficiency

Leukocyte adhesion deficiency results from an adhesion molecule defect that causes granulocyte and lymphocyte dysfunction and recurrent soft-tissue infections.

Inheritance is autosomal recessive. Leukocyte adhesion deficiency is caused by deficiency of adhesive glycoproteins on the surfaces of WBCs; these glycoproteins facilitate cellular interactions, cell attachment to blood vessel walls, cell movement, and interaction with complement fragments. Deficiencies impair the ability of granulocytes (and lymphocytes) to migrate out of the intravascular compartment, to engage in cytotoxic reactions, and to phagocytose bacteria. Severity of disease correlates with degree of deficiency.

Severely affected infants have recurrent or progressive necrotic soft-tissue infections with staphylococcal and gram-negative bacteria, periodontitis, poor wound healing, leukocytosis, and delayed (> 3 wk) umbilical cord detachment. WBC counts remain high even between infections. Infections become increasingly difficult to control.

Diagnosis

Diagnosis is by detecting absence or severe deficiency of adhesive glycoproteins on the surface of WBCs using monoclonal antibodies (eg, anti-CD11, anti-CD18) and flow cytometry. Leukocytosis on CBC is common but nonspecific.

Treatment

Most patients die by age 5 unless treated successfully with bone marrow transplantation, but moderately affected patients survive into young adulthood.

Treatment is with antibiotics, often given continuously. Granulocyte transfusions can also help. Bone marrow transplantation is the only effective treatment and can be curative.

Severe Combined Immunodeficiency

Severe combined immunodeficiency is characterized by absent T cells and a low, high, or normal number of B cells and natural killer cells. Most infants develop opportunistic infections within the first 3 mo of life. Diagnosis is by detecting lymphopenia, absence or a very low number of T cells, and impaired lymphocyte proliferative responses to mitogens. Patients must be kept in a protected environment; definitive treatment is bone marrow stem cell transplantation.

Severe combined immunodeficiency (SCID) is caused by mutations in any one of at least 12 different genes. All but one type are autosomal recessive defects, so for the infant to be affected with SCID, the same gene must be mutated on both chromosomes. There are 4 different abnormal lymphocyte phenotypes. In all forms of SCID, T cells are absent (T-); the number of B cells and natural killer (NK) cells may be low or none (B-; NK-) or high or normal (B+; NK+), depending on the form of SCID. However, B cells, even when normal in number, cannot function because T cells are absent.

The most common form is X-linked. It affects the IL-2 receptor γ chain (a component of at least 6 cytokine receptors) and thus causes severe disease; phenotype is T- B+ NK-. The 2nd most common form results from adenosine deaminase (ADA) deficiency, which leads to apoptosis of precursors for B, T, and NK cells; phenotype is T- B- NK-. The next most common form results from IL-7 receptor α-chain deficiency; phenotype is T- B+ NK+.

Symptoms and Signs

By age 6 mo, most infants with SCID develop candidiasis, persistent viral infections, *Pneumocystis jirovecii* pneumonia, and diarrhea, leading to failure to thrive. Some have graft-vs-host disease due to maternal lymphocytes or blood transfusions. Other infants present at age 6 to 12 mo. Exfoliative dermatitis may develop as part of Omenn's syndrome, one form of SCID. ADA deficiency may cause bone abnormalities. The thymus is extremely small, and lymphoid tissue may be decreased or absent.

All forms of SCID are fatal during infancy unless they are diagnosed and treated early.

Diagnosis

• History of persistent infections

• CBC with differential

• Mitogen and vaccine antigen stimulation assays

• Tests to determine type of SCID

SCID is suspected in infants with a history of persistent infections. CBC, including absolute WBC count and differential, is done; Ig levels are measured. Responses to mitogens and to standard vaccine antigens are determined to evaluate WBC and antibody function. Chest x-rays to evaluate the thymus are not necessary for diagnosis.

The disorder is diagnosed in patients with the following:

• Lymphopenia

• A low number of or no T cells

• Absent lymphocyte proliferative responses to mitogens

Other tests are done to determine the type of SCID. ADA and purine nucleoside phosphorylase levels in WBCs, RBCs, and fibroblasts are measured. X-inactivation tests may be done to determine whether SCID is X-linked.

Treatment

• IV immune globulin (IVIG)

• Antibiotics

• Bone marrow stem cell transplantation

• Sometimes ADA injections or gene therapy

Patients must be kept in reverse isolation. Treatment with IVIG and antibiotics, including *P. jirovecii* prophylaxis, is helpful but not curative.

In 90 to 100% of infants with SCID or its variants, bone marrow stem cell transplantation from an HLA-identical, mixed leukocyte culture-matched sibling restores immunity. When an HLA-identical sibling is not available, haploidentical bone marrow from a parent that is rigorously depleted of T cells can be used. If SCID is diagnosed by age 3 mo, the survival rate after transplantation with either type of bone marrow is 96%. Pretransplantation chemotherapy is unnecessary because patients do not have T cells and therefore cannot reject a graft.

Patients with ADA deficiency who do not receive a bone marrow graft may be treated with injections of polyethylene glycol-modified bovine ADA once or twice/wk. Gene therapy has been successful in X-linked SCID but has caused T-cell leukemias, precluding its use. Gene therapy has also been successful in ADA-deficient SCID, and no posttreatment leukemias or lymphomas have been reported.

Transient Hypogammaglobulinemia of Infancy

Transient hypogammaglobulinemia of infancy is a temporary decrease in serum IgG and sometimes IgA and other Ig isotypes to levels below age-appropriate normal values.

In transient hypogammaglobulinemia of infancy, IgG levels continue to be low after the physiologic fall in maternal IgG at about age 3 to 6 mo. The condition rarely leads to significant infections and is not thought to be a true immunodeficiency.

Diagnosis is based on low serum Ig levels and tests showing that antibody production in response to vaccine antigens (eg, tetanus, diphtheria) is normal. Thus, this condition can be distinguished from permanent forms of hypogammaglobulinemia, in which specific antibodies to vaccine antigens are not produced.

IV immunoglobulin is unnecessary. This condition may persist for months to a few years but usually resolves.

Wiskott-Aldrich Syndrome

Wiskott-Aldrich syndrome results from a combined B- and T-cell defect and is characterized by recurrent infection, atopic dermatitis, and thrombocytopenia.

Inheritance is X-linked recessive. Wiskott-Aldrich syndrome is caused by mutations in the gene that

encodes the Wiskott-Aldrich syndrome protein (WASP), a cytoplasmic protein necessary for normal B- and T-cell signaling. Because B- and T-cell functions are impaired, infections with pyogenic bacteria and opportunistic organisms, particularly viruses and *Pneumocystis jirovecii*, develop.

The first manifestations are often hemorrhagic (usually bloody diarrhea), followed by recurrent respiratory infections, eczema, and thrombocytopenia. Cancers, especially Epstein-Barr virus lymphomas and acute lymphoblastic leukemia, develop in about 10% of patients > 10 yr.

Diagnosis

Diagnosis is based on tests showing impaired antibody responses to polysaccharide antigens, cutaneous anergy, partial T-cell immunodeficiency, elevated IgE and IgA levels, low IgM levels, and low or normal IgG levels. Antibodies to polysaccharide antigens (eg, blood group antigens A and B) may be selectively deficient. Platelets are small and defective, and splenic destruction of platelets is increased, causing thrombocytopenia. Mutation analysis may be used.

Treatment

Treatment is splenectomy, continuous antibiotics, IV immunoglobulin, and bone marrow transplantation. Without transplantation, most patients die by age 15; however, some patients survive into adulthood.

X-linked Agammaglobulinemia

(Bruton's Disease)

X-linked agammaglobulinemia is characterized by low levels or absence of Igs and absent B cells, leading to recurrent infections with encapsulated bacteria.

X-linked agammaglobulinemia results from mutations in a gene on the X chromosome that encodes Bruton tyrosine kinase (Btk). Btk is essential for B-cell development and maturation; without it, there are no B cells and hence no antibodies. As a result, male infants have very small tonsils and do not develop lymph nodes; they have recurrent pyogenic lung, sinus, and skin infections with encapsulated bacteria (eg, *Streptococcus pneumoniae*, *Haemophilus influenzae*). Patients are also susceptible to persistent CNS infections resulting from live-attenuated oral polio vaccine and from echoviruses and coxsackieviruses; these infections can also manifest as progressive dermatomyositis with or without encephalitis.

With early diagnosis and appropriate treatment, prognosis is good unless CNS viral infections develop.

Diagnosis

• Low Ig levels and absent B cells

Diagnosis is by detecting low IgG levels (< 100 mg/dL) and absent B cells (< 1% CD19+ cells via flow cytometry). Transient neutropenia may also be present. If the mutation has been identified in family members, mutational analysis of chorionic villus, amniocentesis, or percutaneous umbilical cord blood samples can provide prenatal diagnosis.

Treatment

Treatment is IV immune globulin 400 mg/kg once/mo. Prompt use of adequate antibiotics for each infection is crucial; bronchiectasis requires continuous rotation of antibiotics.

X-linked Lymphoproliferative Syndrome

(Duncan's Syndrome)

X-linked lymphoproliferative syndrome results from a T-cell and natural killer cell defect and is

characterized by an abnormal response to Epstein-Barr virus infection, leading to liver failure, immunodeficiency, lymphoma, fatal lymphoproliferative disease, or bone marrow aplasia.

X-linked lymphoproliferative syndrome is caused by mutations in a gene on the X chromosome that encodes a T and natural killer (NK) cell-specific protein called SAP. Without SAP, lymphocytes proliferate unchecked in response to Epstein-Barr virus (EBV) infection, and NK cells do not function.

The syndrome is usually asymptomatic until EBV infection develops. Then, most patients develop fulminating or fatal infectious mononucleosis with liver failure (caused by cytotoxic T cells that react to EBV-infected B or other tissue cells); survivors of initial infection develop B-cell lymphomas, aplastic anemia, hypogammaglobulinemia (resembling that in common variable immunodeficiency), or a combination.

Diagnosis

Diagnostic findings in patients that survive initial EBV infection include hypogammaglobulinemia, decreased antibody responses to antigens (particularly to EBV nuclear antigen), impaired T-cell proliferative responses to mitogens, decreased NK-cell function, and an inverted CD4:CD8 ratio. Genetic diagnosis by mutation analysis is possible before EBV infection and symptoms develop.

Treatment

About 75% of patients die by age 10, and all die by age 40 unless bone marrow transplantation is done. Transplantation is curative if done before EBV infection or other disorders become irreversible, resulting in death.

ZAP-70 Deficiency

ZAP-70 (ζ-associated protein 70) deficiency is impaired T-cell activation caused by a signaling defect.

ZAP-70 is important in T-cell signaling and in T-cell selection in the thymus. ZAP-70 deficiency causes T-cell activation defects.

Patients who have ZAP-70 deficiency present during infancy or early childhood with recurrent infections similar to those in severe combined immunodeficiency (SCID); however, they live longer, and the deficiency may not be diagnosed until they are several years old. Patients have normal, low, or elevated serum Ig levels and normal or elevated numbers of circulating CD4 T cells but essentially no CD8 T cells. Their CD4 T cells do not respond to mitogens or allogeneic cells in vitro and do not produce cytotoxic T cells. In contrast, natural killer cell activity is normal.

Diagnosis is similar to that for SCID.

The disorder is fatal unless treated by bone marrow transplantation.

Chapter 127. Allergic and Other Hypersensitivity Disorders

Introduction

Allergic and other hypersensitivity disorders are exaggerated or inappropriate immune reactions.

Classification

The Gell and Coombs classification delineates 4 types of hypersensitivity reaction. Hypersensitivity disorders often involve more than 1 type.

Type I: Type I reactions (immediate hypersensitivity) are IgE-mediated. Antigen binds to IgE (which is bound to tissue mast cells and blood basophils), triggering release of preformed mediators (eg, histamine, proteases, chemotactic factors) and synthesis of other mediators (eg, prostaglandins, leukotrienes, platelet-activating factor, cytokines). These mediators cause vasodilation, increased capillary permeability, mucus hypersecretion, smooth muscle spasm, and tissue infiltration with eosinophils, type 2 helper T cells (T_H2), and other inflammatory cells. Type I reactions underlie atopic disorders (eg, allergic asthma, rhinitis, conjunctivitis) and latex and some food allergies.

Type II: Type II reactions result when antibody binds to cellular or tissue antigens or to a molecule coupled to a cell or tissue. The antigen-antibody complex activates cells that participate in antibody-dependent cell-mediated cytotoxicity (eg, NK cells, eosinophils, macrophages), complement, or both. The result is cell and tissue damage. Disorders involving type II reactions include hyperacute graft rejection of an organ transplant, Coombs'-positive hemolytic anemias, Hashimoto's thyroiditis, and antiglomerular basement membrane disease (eg, Goodpasture's syndrome).

Type III: Type III reactions cause acute inflammation in response to circulating antigen-antibody immune complexes deposited in vessels or tissue. These complexes can activate the complement system or bind to and activate certain immune cells, resulting in release of inflammatory mediators. Consequences of immune complex formation depend in part on the relative proportions of antigen and antibody in the immune complex. Early, there is excess antigen with small antigen-antibody complexes, which do not activate complement. Later, when antigen and antibody are more balanced, immune complexes are larger and tend to be deposited in various tissues (glomeruli, blood vessels), causing systemic reactions. The isotype of induced antibodies changes, and glycosylation of the complex's components contributes to the clinical response. Type III disorders include serum sickness, SLE, RA, leukocytoclastic vasculitis, cryoglobulinemia, hypersensitivity pneumonitis, bronchopulmonary aspergillosis, and several types of glomerulonephritis.

Type IV: Type IV reactions (delayed hypersensitivity) are T cell-mediated. There are 4 subtypes based on the T-cell subpopulation involved:

- IVa: Type 1 helper T cells
- IVb: Type 2 helper T cells
- IVc: Cytotoxic T cells
- IVd: IL-8-secreting T cells

These cells, sensitized after contact with a specific antigen, are activated by reexposure to the antigen; they damage tissue by direct toxic effects or through release of cytokines, which activate eosinophils, monocytes and macrophages, neutrophils, or killer cells depending on type. Disorders involving type IV reactions include contact dermatitis (eg, poison ivy), hypersensitivity pneumonitis, allograft rejection, TB, and many forms of drug hypersensitivity.

Autoimmune disorders: Immune system reactions directed against intrinsic body components can lead to autoimmune disease (see

Table 127-1).

Angioedema

Angioedema is edema of the deep dermis and subcutaneous tissues. It is caused by exposure to drug, venom, dietary, or extracted allergens. The main symptom is diffuse, painful swelling that can be severe. Diagnosis is by examination. Treatment is elimination or avoidance of the allergen and H_1 blockers.

Acute angioedema is essentially anaphylaxis of the subcutaneous tissues. It is sometimes accompanied by urticaria (local wheals and erythema in the skin—see p. 639); the two have similar causes (eg, drug, venom, dietary, or extracted allergens). Also, angioedema is pathogenetically related to urticaria, which occurs at the epidermal-dermal junction.

Chronic (> 6 wk) angioedema is rarely IgE-mediated and is more difficult to explain. Cause is usually unknown (idiopathic), but chronic ingestion of an unsuspected drug or chemical (eg, penicillin in milk, a nonprescription drug, preservatives, other food additives) is sometimes the cause. A few cases are hereditary (see p. 1112).

Symptoms and Signs

Angioedema may be slightly pruritic or nonpruritic. It is characterized by locally diffuse and painful soft-tissue swelling that may be asymmetric, especially on the eyelids, lips (see Plate 57), face, and tongue but also on the back of hands or feet and on the genitals. Edema of the upper airways may cause respiratory distress, and the stridor may be mistaken for asthma. Complete airway obstruction may occur.

Diagnosis

• Clinical evaluation

The cause is often obvious, and diagnostic tests are seldom required because reactions are self-limited and nonrecurrent. No test is particularly useful. Erythropoietic protoporphyria may mimic allergic forms of angioedema and can be distinguished by measuring blood and fecal porphyrins (see p. 817).

Treatment

• Oral prednisone

• Sometimes sc epinephrine

• Sometimes IV antihistamines

[**Table 127-1.** Putative Autommune Disorders]

For acute angioedema, treatment is removing or avoiding the allergen and relieving symptoms (eg, with H_1 blockers—see p. 1116 and Table 127-2). Prednisone 30 to 40 mg po once/day is indicated for more severe reactions. Topical corticosteroids are useless. If a cause is not obvious, all nonessential drugs should be stopped. Pharyngeal or laryngeal angioedema requires epinephrine 0.3 mL of a 1:1000 solution sc. It may be supplemented with an IV anti-histamine (eg, diphenhydramine 50 to 100 mg). Long-term treatment may involve H_1 and H_2 blockers and occasionally corticosteroids.

[**Table 127-2.** Oral H_1 Blockers]

Hereditary Angioedema

Hereditary angioedema is caused by deficiency or dysfunction of C1 inhibitor, a protein that regulates the classical complement activation pathway (see p. 1085).

Hereditary angioedema has 2 types:

• Type 1 (85%): C1 inhibitor is deficient.

• Type 2 (15%): C1 inhibitor malfunctions.

Inheritance is autosomal dominant. C1 inhibitor deficiency may also be acquired: when complement is consumed in neoplastic disorders (eg, B-cell lymphoma), when C1 inhibitor autoantibody is produced in monoclonal gammopathy, or, rarely, when the autoantibody is produced in other disorders (eg, SLE, dermatomyositis). Attacks can be precipitated by mild trauma (eg, dental work, tongue piercing), viral illness, cold exposure, pregnancy, or ingestion of certain foods or may be aggravated by emotional stress.

Symptoms and signs are similar to those of angioedema except that edema progresses until complement components have been consumed; the GI tract is often involved, causing nausea, vomiting, colic, and signs of intestinal obstruction. Other common anatomic locations include the skin and the larynx. Episodes of swelling are self-limited; however, laryngeal involvement can lead to death.

Diagnosis

• Measurement of complement protein levels

Diagnosis is based on detection of low levels of C2 and C4, normal levels of C1q (a fragment of C1), and decreased C1 inhibitor function. In type 1, C1 inhibitor protein levels are low; in type 2, levels are normal or increased. In acquired C1 inhibitor deficiency, C1q levels are low.

Treatment

• Attenuated androgens

• Symptomatic treatments

Attenuated androgens (eg, stanozolol 2 mg po tid, danazol 200 mg po tid) are used to stimulate hepatic C1 inhibitor synthesis. This treatment may be less effective for the acquired form. Some experts advocate giving fresh frozen plasma immediately before dental or medical procedures to prevent attacks, but this approach could theoretically provoke an attack by providing substrate for angioedema.

Purified C1 inhibitor and recombinant C1 inhibitor are being developed for acute treatment. Corticosteroids and antihistamines are not effective. Epinephrine can be of transient benefit in cases of airway involvement. Symptomatic relief can be provided by analgesics, antiemetics, and fluid replacement.

Atopic and Allergic Disorders

Type I hypersensitivity reactions underlie all atopic and many allergic disorders. The terms atopy and allergy are often used interchangeably but are different:

• **Atopy** is an exaggerated IgE-mediated immune response; all atopic disorders are type I hypersensitivity disorders.

• **Allergy** is any exaggerated immune response to a foreign antigen regardless of mechanism.

Thus, all atopic disorders are considered allergic, but many allergic disorders (eg, hypersensitivity pneumonitis) are not atopic. Allergic disorders are the most common disorders among people.

Atopic disorders most commonly affect the nose, eyes, skin, and lungs. These disorders include atopic

dermatitis, contact dermatitis, urticaria (see p. 639), angioedema (which may be primary skin disorders or symptoms of systemic disorders), latex allergy (see Sidebar 127-1), allergic lung disorders (eg, asthma, allergic bronchopulmonary aspergillosis, hypersensitivity pneumonitis), and allergic reactions to venomous stings.

Etiology

Complex genetic, environmental, and site-specific factors contribute to development of allergies.

Genetic factors may be involved, as suggested by familial inheritance of disease, association between atopy and specific HLA loci, and polymorphisms of several genes, including those for the high-affinity IgE receptor β-chain, IL-4 receptor α-chain, IL-4, IL-13, CD14, dipeptidyl-peptidase 10 (DPP10), and a disintegrin and metalloprotease domain 33 (*ADAM33)*.

Environmental factors interact with genetic factors to maintain type 2 helper T (T_H2) cell immune responses, which activate eosinophils and IgE production and are proallergic. Early childhood exposure to bacterial and viral infections and endotoxins (eg, lipopolysaccharide) may normally shift native T_H2-cell responses to type 1 helper T (T_H1)-cell responses, which suppress T_H2 cells and therefore discourage allergic responses. Regulatory T (CD4+CD25+Foxp3+) cells (which are capable of suppressing T_H2-cell responses) and IL-12-secreting dendritic cells (which drive T_H1-cell responses) are perhaps also involved. But trends in developed countries toward smaller families with fewer children, cleaner indoor environments, and early use of vaccinations and antibiotics may deprive children of exposure to infectious agents that drive a predominantly T_H1-cell response; such trends may explain the increased prevalence of some allergic disorders. Other factors thought to contribute to allergy development include chronic allergen exposure and sensitization, diet, and environmental pollutants.

Sidebar 127-1 Latex Sensitivity

Latex sensitivity is an exaggerated immune response to water-soluble proteins in latex products (eg, rubber gloves, dental dams, condoms, tubing for respiratory equipment, catheters, enema tips with inflatable latex cuffs), causing urticaria, angioedema, and anaphylaxis.

Reactions to latex may be acute (IgE-mediated) or delayed (cell-mediated). Acute reactions cause urticaria and anaphylaxis; delayed reactions cause dermatitis.

Diagnosis is based on history. Assays for detecting IgE anti-latex antibodies and patch tests for detecting anti-latex cellular immunity are being developed, but none is well-validated yet.

Treatment is avoidance of latex.

Site-specific factors include adhesion molecules in bronchial epithelium and in skin and molecules in the GI tract that direct T_H2 cells to target tissues.

Allergens: By definition, an allergen induces IgE-mediated and T_H2-cell immune responses. Allergic triggers are almost always low molecular weight proteins; many of them can be constituted as airborne particles.

Allergens that most commonly cause acute and chronic allergic reactions include

- House dust
- Mite feces
- Animal dander

• Pollens (tree, grass, weed)

• Molds

Pathophysiology

When allergen binds to IgE-sensitized mast cells and basophils, histamine is released from their intracellular granules. Mast cells are widely distributed but are most concentrated in skin, lungs, and GI mucosa; histamine facilitates inflammation and is the primary mediator of clinical atopy. Physical disruption of tissue and various substances (eg, tissue irritants, opioids, surface-active agents, complement components C3a and C5a) can trigger histamine release directly, independent of IgE.

Histamine causes the following:

• Local vasodilation (causing erythema)

• Increased capillary permeability and edema (producing a wheal)

• Surrounding arteriolar vasodilation mediated by neuronal reflex mechanisms (causing flare)

• Stimulation of sensory nerves (causing itching)

• Smooth muscle contraction in the airways (bronchoconstriction) and in the GI tract (increasing GI motility)

• Increased salivary and bronchial gland secretions

When released systemically, histamine is a potent arteriolar dilator and can cause extensive peripheral pooling of blood and hypotension; cerebral vasodilation may be a factor in vascular headache. Histamine increases capillary permeability; the resulting loss of plasma and plasma proteins from the vascular space can worsen circulatory shock. This loss triggers a compensatory catecholamine surge from adrenal chromaffin cells.

Symptoms and Signs

Common symptoms include rhinorrhea, sneezing, and nasal congestion (upper respiratory tract); wheezing and dyspnea (lower respiratory tract); and itching (eyes and skin).

Signs may include nasal turbinate edema, sinus pain during palpation, wheezing, conjunctival hyperemia and edema, and skin lichenification. Stridor, wheezing, and sometimes hypotension are life-threatening signs of anaphylaxis (see p. 1120). In some children, a narrow and high-arched palate, narrow chin, and elongated maxilla with overbite (allergic facies) are thought to be associated with chronic allergy.

Diagnosis

• Clinical evaluation

• CBC and serum IgE levels (nonspecific tests)

• Skin testing and radioallergosorbent testing (specific tests)

• Rarely, provocative testing

A thorough history is generally more reliable than testing or screening. History should include

• Questions about frequency and duration of attacks and changes over time

• Triggering factors if identifiable

- Relation to seasonal or situational settings (eg, predictably occurring during pollen seasons; after exposure to animals, hay, or dust; during exercise; or in particular places)

- Family history of similar symptoms or of atopic disorders

- Responses to attempted treatments

Age at onset may be important in asthma because childhood asthma is likely to be atopic and asthma beginning after age 30 is not.

Nonspecific tests: Certain tests can suggest but not confirm an allergic origin of symptoms.

CBC should be ordered to detect eosinophilia in all patients except those taking corticosteroids, which reduce the eosinophil count. An eosinophil differential of 5 to 15% of total WBCs suggests atopy but is nonspecific; 16 to 40% may reflect atopy or other conditions (eg, drug hypersensitivity, cancer, autoimmune disorders, parasitic infection); a differential of 50 to 90% almost never occurs in atopic disorders and is more characteristic of hypereosinophilic syndrome or visceral larva migrans. Total WBC is usually normal.

Conjunctival or nasal secretions or sputum can be examined for leukocytes; finding any eosinophils indicates that T_H2-mediated allergic inflammation is likely.

Serum IgE levels are elevated in atopic disorders but are of little help in diagnosis because they may also be elevated in parasitic infections, infectious mononucleosis, autoimmune disorders, drug reactions, immunodeficiency disorders (hyper-IgE syndrome—see p. 1104—and Wiskott-Aldrich syndrome—see p. 1107), and in some forms of multiple myeloma. IgE levels are probably most helpful for following response to therapy in allergic bronchopulmonary aspergillosis (see p. 1887).

Specific tests: Skin testing uses standardized concentrations of antigen introduced directly into skin and is indicated when a detailed history and physical examination do not identify the cause and triggers for symptoms. Skin testing has higher positive predictive values for diagnosing allergic rhinosinusitis and conjunctivitis than for diagnosing allergic asthma or food allergy; negative predictive value for food allergy is high. The most commonly used antigens are pollens (tree, grass, weed), molds, house dust mites, animal danders and sera, insect venom, foods, and β-lactam antibiotics. Choice of antigens to include is based on patient history and geographic prevalence.

Two skin test techniques can be used

- Percutaneous (prick)

- Intradermal

The prick test can detect most allergies. The intradermal test is more sensitive but less specific; it can be used to evaluate sensitivity to allergens with negative or equivocal prick test results.

For the **prick test**, a drop of antigen extract is placed on the skin, which is then pricked or punctured through the extract by tenting up the skin with the tip of a 27-gauge needle held at a 20° angle or with a commercially available prick device.

For the **intradermal test**, just enough extract to produce a 1- or 2-mm bleb (typically 0.02 mL) is injected intradermally with a 0.5- or 1-mL syringe and a 27-gauge short-bevel needle.

Prick and intradermal skin testing should include the diluent alone as a negative control and histamine (10 mg/mL for prick tests, 0.01 mL of a 1:1000 solution for intradermal tests) as a positive control. For patients who have had a recent (< 1 yr) generalized reaction to the test antigen, testing begins with the standard reagent diluted 100-fold, then 10-fold, and then the standard concentration. A test is considered positive if a wheal and flare reaction occurs and wheal diameter is 3 to 5 mm greater than that of the

negative control after 15 to 20 min. False positives occur in dermatographism (a wheal and flare reaction provoked by stroking or scraping the skin). False negatives occur when allergen extracts have been stored incorrectly or are outdated. Certain drugs can also interfere with results and should be stopped a few days to a week before testing. These drugs include OTC and prescription antihistamines, tricyclic antidepressants, and monoamine oxidase inhibitors. Patients taking β-blockers should not be tested.

Radioallergosorbent testing (RAST) detects the presence of allergen-specific serum IgE and is indicated when skin testing is contraindicated because of generalized dermatitis, dermatographism, history of anaphylaxis to the allergen, or need to continue antihistamines. A known allergen in the form of an insoluble polymer-allergen conjugate is mixed with the serum to be tested and with ^{125}I-labeled anti-IgE antibody. Any allergen-specific IgE in the serum binds the conjugate and can be quantified by measuring the ^{125}I-labeled antibody.

Provocative testing involves direct exposure of the mucosae to allergen and is indicated for patients who must document their reaction (eg, for occupational or disability claims) and sometimes for diagnosis of food allergy.

Ophthalmic testing has no advantage over skin testing and is rarely used.

Nasal and bronchial challenge are primarily research tools, but bronchial challenge is sometimes used when the clinical significance of a positive skin test is unclear or when no antigen extracts are available (eg, for occupation-related asthma).

Treatment

• Removal or avoidance of allergic triggers

• Antihistamines

• Mast cell stabilizers

• Anti-inflammatory corticosteroids and leukotriene inhibitors

• Immunotherapy (desensitization)

Environmental control: Removal or avoidance of allergic triggers is the primary treatment for allergy, as well as the primary preventive strategy (see Prevention on p. 1117).

Antihistamines: Antihistamines block receptors; they do not affect histamine production or metabolism. H_1 blockers are a mainstay of treatment for allergic disorders. H_2 blockers are used primarily for gastric acid suppression and have limited usefulness for allergic reactions; they may be indicated for certain atopic disorders, especially chronic urticaria.

Oral H_1 blockers relieve symptoms in various atopic and allergic disorders (eg, seasonal hay fever, allergic rhinitis, conjunctivitis, urticaria, other dermatoses, minor reactions to blood transfusion incompatibilities and to x-ray radiopaque dyes); they are less effective for allergic bronchoconstriction and vasodilation. Onset of action is usually 15 to 30 min, with peak effects in 1 h; duration of action is usually 3 to 6 h.

Oral H_1 blockers are classified as sedating or nonsedating (better thought of as less sedating). Sedating antihistamines are widely available without prescription. All have significant sedative and anticholinergic properties; they pose particular problems for the elderly and for patients with glaucoma, benign prostatic hyperplasia, constipation, or dementia. Nonsedating (nonanticholinergic) antihistamines are preferred except when sedative effects may be therapeutic (eg, for nighttime relief of allergy, for short-term treatment of insomnia in adults or nausea in younger patients). Anticholinergic effects may also partially justify use of sedating antihistamines to relieve rhinorrhea in URIs.

Antihistamine solutions may be intranasal (azelastine to treat rhinitis) or ocular (azelastine, emedastine, ketotifen, levocabastine, or olopatadine to treat conjunctivitis). Topical diphenhydramine is available but should not be used; its efficacy is unproved, drug sensitization (ie, allergy) may occur, and anticholinergic toxicity can develop in young children who are simultaneously taking oral H_1 blockers.

Mast cell stabilizers: These drugs (eg, cromolyn) block the release of mediators from mast cells; they are used when other drugs (eg, antihistamines, topical corticosteroids) are ineffective or not well tolerated. Ocular forms (eg, lodoxamide, olopatadine, pemirolast) are also available.

Anti-inflammatory drugs: Corticosteroids can be given intranasally (see Table 127-3) or orally. Oral corticosteroids are indicated for systemic allergic disorders that are severe but self-limited (eg, seasonal asthma flares, severe widespread contact dermatitis) and for disorders refractory to other measures. NSAIDs are typically not useful, with the exception of topical ketorolac for allergic conjunctivitis.

Leukotriene modifiers are indicated for treatment of mild persistent asthma (see p. 1881) and seasonal allergic rhinitis.

Anti-IgE antibody (omalizumab) is indicated for moderately persistent or severe asthma refractory to standard treatment (see p. 1881).

Immunotherapy: Exposure to allergen in gradually increasing doses (hyposensitization or desensitization) via injection or in high doses sublingually can induce tolerance

[**Table 127-3.** Inhaled Nasal Corticosteroids and Mast Cell Stabilizers]

and is indicated when allergen exposure cannot be avoided and drug treatment is inadequate. Mechanism is unknown but may involve induction of IgG antibodies, which compete with IgE for allergen or block IgE from binding with mast cell IgE receptors; induction of interferon-γ, IL-12, and cytokines secreted by TH_1 cells; or induction of regulatory T cells.

For full effect, injections must be given monthly. Dose typically starts at 0.1 to 1.0 biologically active units (BAU), depending on initial sensitivity, and is increased weekly or biweekly by ≤ 2 times with each injection until a maximum tolerated concentration is reached; *patients should be observed for about 30 min postinjection during dose escalation because anaphylaxis may occur after injection*. Maximum dose should be given q 4 to 6 wk year-round; year-round treatment is better than preseasonal or coseasonal treatment even for seasonal allergies. Allergens used are those that typically cannot be avoided: pollens, house dust mites, molds, and venom of stinging insects. Insect venoms are standardized by weight; a typical starting dose is 0.01 µg, and usual maintenance dose is 100 to 200 µg. Animal dander desensitization is ordinarily limited to patients who cannot avoid exposure (eg, veterinarians, laboratory workers), but there is little evidence that it is useful. Food desensitization is not indicated. Desensitization for penicillin and certain other antibiotics and for foreign (xenogeneic) serum can be done (see p. 1120).

Adverse effects are most commonly related to overdose, occasionally via an inadvertent IM or IV injection, and range from mild cough or sneezing to generalized urticaria, severe asthma, anaphylactic shock, and, rarely, death. They can be prevented by the following:

- Increasing the dose in small increments
- Repeating or decreasing the dose if local reaction to the previous injection is large (≥ 2.5 cm in diameter)
- Reducing the dose when a fresh extract is used

Reducing the dose of pollen extract during pollen season is recommended. Epinephrine, O_2, and resuscitation equipment should be immediately available for prompt treatment of anaphylaxis.

Prevention

Allergic triggers should be removed or avoided. Strategies include the following:

• Using synthetic fiber pillows and impermeable mattress covers

• Frequently washing bed sheets, pillowcases, and blankets in hot water

• Removing upholstered furniture, soft toys, carpets, and pets

• House cleaning and extermination to eliminate cockroach exposure

• Using dehumidifiers in basements and other poorly aerated, damp rooms

• Treating homes with heat-steam

• Using high-efficiency particulate air (HEPA) vacuums and filters

• Avoiding food triggers

• Limiting pets to certain rooms

• Frequently cleaning cloth furniture and carpets

Adjunctive nonallergenic triggers (eg, cigarette smoke, strong odors, irritating fumes, air pollution, cold temperatures, high humidity) should also be avoided or controlled when possible.

Allergic Rhinitis

Allergic rhinitis is seasonal or perennial itching, sneezing, rhinorrhea, nasal congestion, and sometimes conjunctivitis, caused by exposure to pollens or other allergens. Diagnosis is by history and skin testing. Treatment is with a combination of antihistamines, decongestants, nasal corticosteroids, and, for severe, refractory cases, desensitization.

Allergic rhinitis may occur seasonally (hay fever) or throughout the year (perennial rhinitis). At least 25% of perennial rhinitis is nonallergic.

Seasonal rhinitis is caused by

• **Spring:** Tree pollens (eg, oak, elm, maple, alder, birch, juniper, olive)

• **Summer:** Grass pollens (eg, Bermuda, timothy, sweet vernal, orchard, Johnson) and weed pollens (eg, Russian thistle, English plantain)

• **Fall:** Other weed pollens (eg, ragweed)

Causes also differ by region, and seasonal rhinitis is occasionally caused by airborne fungal spores. Perennial rhinitis is caused by year-round exposure to indoor inhaled allergens (eg, dust mites, cockroaches, animal dander, mold) or by strong reactivity to plant pollens in sequential seasons.

Allergic rhinitis and asthma frequently coexist; whether rhinitis and asthma result from the same allergic process (one-airway hypothesis) or rhinitis is a discrete asthma trigger is unclear.

Nonallergic forms of perennial rhinitis include infectious, vasomotor, atrophic, hormonal, drug-induced, and gustatory rhinitis (see p. 478).

Symptoms and Signs

Patients have itching (in the nose, eyes, or mouth), sneezing, rhinorrhea, and nasal and sinus obstruction. Sinus obstruction may cause frontal headaches; sinusitis is a frequent complication. Coughing and wheezing may also occur, especially if asthma is also present.

The most prominent feature of perennial rhinitis is chronic nasal obstruction, which, in children, can lead to chronic otitis media; symptoms vary in severity throughout the year. Itching is less prominent than in seasonal rhinitis.

Signs include edematous, bluish-red nasal turbinates, and, in some cases of seasonal rhinitis, conjunctival injection and eyelid edema.

Diagnosis

• Clinical evaluation

• Sometimes skin testing, RAST, or both

Allergic rhinitis can almost always be diagnosed based on history alone. Diagnostic testing is not routinely needed unless patients do not improve when treated empirically; for such patients, skin tests are done to identify a reaction to pollens (seasonal) or to dust mite, cockroach, animal dander, mold, or other antigens (perennial), which can be used to guide additional treatment. Occasionally, skin test results are ambivalent, or testing cannot be done (eg, because patients are taking drugs that interfere with results); then, RAST is done. Eosinophilia detected on nasal smear plus negative skin tests suggests aspirin sensitivity or nonallergic rhinitis with eosinophilia (NARES).

Diagnosis of infectious, vasomotor, atrophic, hormonal, drug-induced, and gustatory rhinitis is usually based on history or therapeutic trials.

Treatment

• Removal or avoidance of allergens for perennial rhinitis

• Antihistamines, decongestants, nasal corticosteroids, or a combination

• Sometimes immunotherapy for seasonal rhinitis

• Desensitization for severe, refractory rhinitis

Treatment of seasonal and perennial allergic rhinitis is generally the same, although attempts at environmental control (eg, eliminating dust mites and cockroaches) are recommended for perennial rhinitis.

The most effective first-line drug treatments are

• Oral antihistamines plus oral decongestants

• Nasal corticosteroids with or without oral antihistamines (see Table 127-3)

Less effective alternatives include nasal mast cell stabilizers (eg, cromolyn) given bid to qid, the nasal H_1 blocker azelastine 2 puffs once/day, and nasal ipratropium 0.03% 2 puffs q 4 to 6 h, which relieves rhinorrhea. Intranasal saline, often forgotten, helps mobilize thick nasal secretions and hydrate nasal mucous membranes.

Immunotherapy may be more effective for seasonal than for allergic perennial rhinitis; it is indicated when symptoms are severe, allergen cannot be avoided, and drug treatment is inadequate.

Desensitization may be needed for severe, refractory rhinitis. First attempts at desensitization should

begin soon after the pollen season ends to prepare for the next season; adverse reactions increase when desensitization is started during the pollen season because the person's allergic immunity is already maximally stimulated.

Montelukast relieves allergic rhinitis symptoms, but its role relative to other treatments is uncertain. Anti-IgE antibody is under study for treatment of allergic rhinitis but will probably have a limited role because less expensive, effective alternatives are available.

Treatment of NARES is nasal corticosteroids. Treatment of aspirin sensitivity is aspirin avoidance, with desensitization and leukotriene blockers as needed. Nasal polyps may respond to nasal corticosteroids.

Food Allergy

Food allergy is an exaggerated immune response to dietary proteins.

Food allergy should be distinguished from nonimmune reactions to food (eg, lactose intolerance, irritable bowel syndrome, infectious gastroenteritis) and reactions to additives (eg, monosodium glutamate, metabisulfite, tartrazine) or food contaminants (eg, latex dust in food handled by workers wearing latex gloves), which cause most food reactions. Prevalence of true food allergy ranges from < 1 to 3% and varies by geography and method of ascertainment; patients tend to confuse intolerance with allergy.

Etiology

Almost any food or food additive can cause an allergic reaction, but the most common triggers include

• **Infants and young children:** Milk, soy, eggs, peanuts, and wheat

• **Older children and adults:** Nuts and seafood

Cross-reactivity between food and nonfood allergens exists, and sensitization may occur nonenterally. For example, patients with oral allergies (typically, pruritus, erythema, and edema of the mouth when fruits and vegetables are eaten) may have been sensitized by pollen exposure; children with peanut allergy may have been sensitized by topical creams containing peanut oil used to treat rashes. Many patients who are allergic to latex are also allergic to bananas, kiwis, avocadoes, or a combination.

In general, food allergy is mediated by IgE, T cells, or both. IgE-mediated allergy (eg, urticaria, asthma, anaphylaxis) is acute in onset, usually develops during infancy, and occurs most often in people with a strong family history of atopy. T cell-mediated allergy (eg, dietary protein gastroenteropathies, celiac disease) manifests gradually and is chronic. Allergies mediated by both IgE and T cells (eg, atopic dermatitis, eosinophilic gastroenteropathy) tend to be delayed in onset or chronic.

Eosinophilic gastroenteropathy: This unusual disorder causes pain, cramps, and diarrhea with blood eosinophilia, eosinophilic infiltrates in the gut, protein-losing enteropathy, and a history of atopic disorders. Eosinophilic esophagitis sometimes accompanies eosinophilic gastroenteropathy. Initially, it may cause dysphagia and dysmotility or, in children, feeding intolerance and abdominal pain.

Symptoms and Signs

Symptoms and signs vary by allergen, mechanism, and patient age. The most common manifestation in infants is atopic dermatitis alone or with GI symptoms (nausea, vomiting, diarrhea). Children usually outgrow these manifestations and react increasingly to inhaled allergens, with symptoms of asthma and rhinitis; this progression is called atopic march. By age 10 yr, patients rarely have respiratory symptoms after the allergenic food is eaten, even though skin tests remain positive. If atopic dermatitis persists or appears in older children or adults, its activity seems largely independent of IgE-mediated allergy, even though atopic patients with extensive dermatitis have much higher serum IgE levels than those who are free of dermatitis.

When food allergy persists in older children and adults, reactions tend to be more severe (eg, explosive

urticaria, angioedema, even anaphylaxis). In a few patients, food (especially wheat and celery) triggers anaphylaxis only if they exercise soon afterward; mechanism is unknown. A few patients have food-induced or aggravated migraine, confirmed by blinded oral challenge. Occasionally, cheilitis, aphthae, pylorospasm, spastic constipation, pruritus ani, and perianal eczema are attributed to food allergy.

Diagnosis

• Skin testing or RAST

• Trial elimination diet (alone or after skin testing or RAST)

Severe food allergy is usually obvious in adults. When it is not and when it occurs in children (usually), diagnosis may be difficult, and the disorder must be differentiated from functional GI problems.

If a food reaction is suspected, the relationship of symptoms to foods is assessed by skin testing or IgE-specific RAST. A positive test does not confirm a clinically relevant allergy, but a negative test excludes it. If a skin test is positive, the tested food is eliminated from the diet; if symptoms are relieved, the patient is reexposed to the food (preferably in a double-blind test) to see whether symptoms recur.

Alternatives to skin testing include eliminating foods the patient suspects of causing symptoms and prescribing a diet that consists of relatively nonallergenic foods and that eliminates common food allergens (see Table 127-4). No foods or fluids may be consumed other than those specified. Pure products must always be used. Many commercially prepared products and meals contain an undesired food in large amounts (eg, commercial rye bread contains wheat flour) or in traces as flavoring or thickeners, and determining whether an undesired food is present may be difficult.

If no improvement occurs after 1 wk, another diet should be tried. If symptoms are relieved, one new food is added and eaten in large amounts for > 24 h or until symptoms recur. Alternatively, small amounts of the food to be tested are eaten in the clinician's presence, and the patient's reactions observed. Aggravation or recrudescence of symptoms after addition of a new food is the best evidence of allergy.

Treatment

• Food elimination diet

• Sometimes oral cromolyn

• Sometimes corticosteroids for eosinophilic enteropathy

[**Table 127-4.** Allowable Foods in Elimination Diets*]

Treatment consists of eliminating the food that triggers the allergic reaction. Thus, diagnosis and treatment overlap. When assessing an elimination diet's effect, clinicians must consider that food sensitivities may disappear spontaneously.

Oral desensitization (by first eliminating the allergenic food for a time, then giving small amounts and increasing them daily) is not effective nor is use of sublingual drops of food extracts. Antihistamines are of little value except in acute general reactions with urticaria and angioedema. Oral cromolyn has been used with apparent success. Prolonged corticosteroid treatment is helpful for symptomatic eosinophilic enteropathy.

Anaphylaxis

Anaphylaxis is an acute, life-threatening, IgE-mediated allergic reaction that occurs in previously sensitized people when they are reexposed to the sensitizing antigen. Symptoms include stridor, dyspnea, wheezing, and hypotension. Diagnosis is clinical. Bronchospasm and upper airway edema are treated with inhaled or injected β-agonists and sometimes

endotracheal intubation. Hypotension requires IV fluids and vasopressors.

Etiology

Anaphylaxis is typically triggered by

• Drugs (eg, β-lactam antibiotics, insulin, streptokinase, allergen extracts)

• Foods (eg, nuts, eggs, seafood)

• Proteins (eg, tetanus antitoxin, blood transfusions)

• Animal venoms

• Latex

Peanut and latex allergens may be airborne. History of atopy does not increase risk of anaphylaxis but increases risk of death when anaphylaxis occurs.

Pathophysiology

Interaction of antigen with IgE on basophils and mast cells triggers release of histamine, leukotrienes, and other mediators that cause diffuse smooth muscle contraction (bronchoconstriction, vomiting, diarrhea) and vasodilation with plasma leakage.

Anaphylactoid reactions: These reactions are clinically indistinguishable from anaphylaxis but do not involve IgE and do not require prior sensitization. They occur via direct stimulation of mast cells or via immune complexes that activate complement. The most common triggers are iodinated radiographic radiopaque dye, aspirin, other NSAIDs, opioids, blood transfusions, Ig, and exercise.

Symptoms and Signs

Symptoms typically involve the skin, upper or lower airways, cardiovascular system, or GI tract. One or more areas may be affected, and symptoms do not necessarily progress, although each patient typically manifests the same reaction to subsequent exposure.

Symptoms range from mild to severe and include flushing, pruritus, sneezing, rhinorrhea, nausea, abdominal cramps, diarrhea, sense of choking or dyspnea, palpitations, and dizziness.

Signs include hypotension, tachycardia, urticaria, angioedema, wheezing, cyanosis, and syncope. Shock can develop within minutes, and patients may experience seizures, become unresponsive, and die. Cardiovascular collapse can occur without respiratory or other symptoms.

Diagnosis

Diagnosis is clinical. Risk of rapid progression to shock leaves no time for testing, although mild equivocal cases can be confirmed by measuring 24-h urinary levels of *N*-methylhistamine or serum levels of tryptase.

Treatment

• Epinephrine given immediately

• Sometimes intubation

• IV fluids and vasopressors for hypotension

• Antihistamines

• Inhaled β-agonists for bronchoconstriction

Epinephrine is the cornerstone of treatment and should be given immediately. It can be given sc or IM (usual dose is 0.3 to 0.5 mL of a 1:1000 solution in adults or 0.01 mL/kg in children, repeated every 10 to 30 min); maximal absorption occurs when the drug is given IM in the lateral thigh. Patients with cardiovascular collapse or severe airway obstruction may be given epinephrine IV in a single dose (3 to 5 mL of a 1:10,000 solution over 5 min) or by continuous drip (1 mg in 250 mL 5% D/W for a concentration of 4 µg/mL, starting at 1 µg/min up to 4 µg/min [15 to 60 mL/h]). Epinephrine may also be given by sublingual injection (0.5 mL of 1:1000 solution) or through an endotracheal tube (3 to 5 mL of a 1:10,000 solution diluted to 10 mL with saline). A 2nd injection of epinephrine sc may be needed. Glucagon 1-mg bolus followed by 1-mg/h infusion should be used in patients taking oral β-blockers, which attenuate the effect of epinephrine.

Patients who have stridor and wheezing unresponsive to epinephrine should be given O_2 and be intubated. Early intubation is recommended because waiting for a response to epinephrine may allow upper airway edema to progress sufficiently to prevent endotracheal intubation and require cricothyrotomy.

Hypotension can usually be treated with 1 to 2 L (20 to 40 mL/kg in children) of isotonic IV fluids (eg, 0.9% saline). Hypotension refractory to fluids and IV epinephrine may require vasopressors (eg, dopamine 5 µg/kg/min).

Antihistamines—both H_1 blockers (eg, diphenhydramine 50 to 100 mg IV) and H_2 blockers (eg, cimetidine 300 mg IV)—should be given q 6 h until symptoms resolve. Inhaled β-agonists are useful for managing bronchoconstriction; albuterol 5 to 10 mg by continuous nebulization can be given.

Corticosteroids have no proven role but may help prevent late-phase reaction in 4 to 8 h; methylprednisolone 125 mg IV initially is adequate.

Prevention

Primary prevention is avoidance of known triggers. Desensitization is used for allergen triggers that cannot reliably be avoided (eg, insect stings). Patients with past reactions to radiopaque dye should not be reexposed; when exposure is absolutely necessary, patients are given 3 doses of prednisone 50 mg po q 6 h, starting 18 h before the procedure, and diphenhydramine 50 mg po 1 h before the procedure; however, no evidence supports the efficacy of this approach (see also p. 3404).

Patients with an anaphylactic reaction to insect stings, foods, or other known substances should wear an alert bracelet and carry a prefilled epinephrine syringe (containing 0.3 mg for adults and 0.15 mg for children) for prompt self-treatment after exposure.

Autoimmune Disorders

In autoimmune disorders, the immune system produces antibodies to an endogenous antigen. It may involve the following hypersensitivity reactions:

• **Type II:** Antibody-coated cells, like any similarly coated foreign particle, activate the complement system (see p. 1085), resulting in tissue injury.

• **Type III:** The mechanism of injury involves deposition of antibody-antigen complexes.

• **Type IV:** Injury is T-cell-mediated.

For specific autoimmune disorders, see elsewhere in THE MANUAL and also Table 127-1.

Etiology

Several mechanisms may account for the body's attack on itself.

Autoantigens may become immunogenic because they are altered chemically, physically, or biologically. Certain chemicals can couple with body proteins, making them immunogenic (as in contact dermatitis). Drugs can produce several autoimmune reactions by binding covalently to serum or tissue proteins (see below). Photosensitivity exemplifies physically induced autoimmunity: Ultraviolet light alters skin protein, to which the patient becomes allergic. In animal models, persistent infection with an RNA virus that combines with host tissues alters autoantigens biologically, resulting in an autoimmune disorder resembling SLE.

Antibodies produced in response to a foreign antigen may cross-react with normal autoantigens (eg, cross-reaction between streptococcal M protein and human heart muscle).

Normally, potentially pathologic autoimmune reactions are avoided because of the immunologic tolerance mechanisms of clonal deletion and clonal anergy. Any autoreactive lymphocytes not controlled by these mechanisms are usually restrained by Foxp3+ regulatory T cells. A regulatory T-cell defect may accompany any of these mechanisms for autoimmunity. Anti-idiotype antibodies (antibodies to the antigen-combining site of other antibodies) may interfere with regulation of antibody activity.

Genetic factors play a role. Relatives of patients with autoimmune disorders often have the same type of autoantibodies, and incidence of autoimmune disorders is higher in identical than in fraternal twins. Most autoimmune disorders have a polygenic etiology, and allelic variants within the HLA gene locus nearly always contribute. Women are affected more often than men. In genetically predisposed people, environmental factors may provoke disease (eg, certain drugs can trigger hemolytic anemia in patients with G6PD deficiency).

Drug Hypersensitivity

Drug hypersensitivity is an immune-mediated reaction to a drug. Symptoms range from mild to severe and include skin rash, anaphylaxis, and serum sickness. Diagnosis is clinical; skin testing is occasionally useful. Treatment is drug discontinuation, antihistamines (for symptoms), and sometimes desensitization.

Drug hypersensitivity must be distinguished from toxic and adverse effects that may be expected from the drug and from problems due to drug interactions (see p. 3167).

Pathophysiology

Some protein and large polypeptide drugs (eg, insulin, therapeutic antibodies) can directly stimulate antibody production. However, most drugs act as haptens, binding covalently to serum or cell-bound proteins, including peptides embedded in major histocompatibility complex (MHC) molecules. The binding makes the protein immunogenic, stimulating antidrug antibody production, T-cell responses against the drug, or both. Haptens may also bind directly to the MHC II molecule, directly activating T cells. When metabolized, prohaptens become haptens; eg, penicillin itself is not antigenic, but its main degradation product, benzylpenicilloic acid, can combine with tissue proteins to form benzylpenicilloyl (BPO), a major antigenic determinant. Some drugs bind and stimulate T-cell receptors (TCR) directly; the clinical significance of nonhapten TCR binding is being determined.

How primary sensitization occurs and how the immune system is initially involved is unclear, but once a drug stimulates an immune response, cross-reactions within and between drug classes can occur. For example, penicillin-sensitive patients are highly likely to react to semisynthetic penicillins (eg, amoxicillin, carbenicillin, ticarcillin), and about 10% react to cephalosporins, which have a similar β-lactam structure. However, some apparent cross-reactions (eg, between sulfonamide antibiotics and nonantibiotics) are due to a predisposition to allergic reactions rather than to specific immune cross-reactivity. Also, not every apparent reaction is allergic; for example, amoxicillin causes a rash that is not immune-mediated and does not preclude future use of the drug.

Symptoms and Signs

Symptoms and signs vary by patient and drug, and a single drug may cause different reactions in different patients. The most serious is anaphylaxis; exanthema (eg, morbilliform eruption), urticaria, and fever are common. Fixed drug reactions are uncommon.

Some distinct clinical syndromes exist.

- **Serum sickness:** This reaction typically occurs 7 to 10 days after exposure and causes fever, arthralgias, and rash. Mechanism involves drug-antibody complexes and complement activation. Some patients have frank arthritis, edema, or GI symptoms. Symptoms are self-limited, lasting 1 to 2 wk. β-Lactam and sulfonamide antibiotics, iron-dextran, and carbamazepine are most commonly implicated.

- **Hemolytic anemia:** This disorder may develop when an antibody-drug-RBC interaction occurs or when a drug (eg, methyldopa) alters the RBC membrane, uncovering an antigen that induces autoantibody production.

- **Pulmonary effects:** Some drugs induce respiratory symptoms, deterioration in pulmonary function, and other pulmonary changes (see p. 1952).

- **Renal effects:** Tubulointerstitial nephritis is the most common allergic renal reaction (see p. 2414); methicillin, antimicrobials, and cimetidine are commonly implicated.

- **Other autoimmune phenomena:** Hydralazine and procainamide can cause an SLE-like syndrome. The syndrome is relatively benign, sparing the kidneys and CNS; the antinuclear antibody test is positive. Penicillamine can cause SLE and other autoimmune disorders (eg, myasthenia gravis).

Diagnosis

- Patient's report of a reaction soon after taking a drug

- Skin testing

- Sometimes drug provocation testing

- Sometimes direct and indirect antiglobulin assays

Drug hypersensitivity is suggested when a reaction occurs within minutes to hours after drug administration. However, many patients report a past reaction of uncertain nature. In such cases, if there is no equivalent substitute (eg, when penicillin is needed to treat syphilis), testing should be considered.

Skin testing: Tests for immediate-type (IgE-mediated) hypersensitivity help identify reactions to β-lactam antibiotics, foreign (xenogeneic) serum, and some vaccines and polypeptide hormones. However, typically, only 10 to 20% of patients who report a penicillin allergy have a positive reaction on skin tests. Also, for most drugs (including cephalosporins), skin tests are unreliable and, because they detect only IgE-mediated reactions, do not predict the occurrence of morbilliform eruptions, hemolytic anemia, or nephritis.

Penicillin skin testing is needed if patients with a history of an immediate hypersensitivity reaction must take a penicillin. BPO-polylysine conjugate and penicillin G are used with histamine and saline as controls. The prick test (see p. 1115) is used first. If patients have a history of a severe explosive reaction, reagents should be diluted 100-fold for initial testing. If prick tests are negative, intradermal testing may follow. If skin tests are positive, treating patients with penicillin may induce an anaphylactic reaction. If tests are negative, a serious reaction is less likely but not excluded. Although the penicillin skin test has not induced de novo sensitivity in patients, patients should usually be tested only immediately before essential penicillin therapy is begun.

For xenogeneic serum skin testing, patients who are not atopic and who have not received xenogeneic (eg, horse) serum previously should first be given a prick test with a 1:10 dilution; if this test is negative,

0.02 mL of a 1:1000 dilution is injected intradermally. A wheal > 0.5 cm in diameter develops within 15 min in sensitive patients. All patients who may have received serum previously—whether or not they reacted—and those with a suspected allergic history should be tested first with a 1:1000 dilution. A negative result rules out the possibility of anaphylaxis but does not predict incidence of subsequent serum sickness.

Other testing: For drug provocation testing, a drug suspected of causing a hypersensitivity reaction is given in escalating doses to precipitate the reaction. This test is probably safe and effective if done in a controlled setting.

Tests for hematologic drug reactions include direct and indirect antiglobulin tests (see p. 937). Tests for other specific drug hypersensitivity (eg, radioallergosorbent testing [RAST], histamine release, basophil or mast cell degranulation, lymphocyte transformation) are unreliable or experimental.

Prognosis

Hypersensitivity decreases with time. IgE antibodies are present in 90% of patients 1 yr after an allergic reaction but in only about 20 to 30% after 10 yr. Patients who have anaphylactic reactions are more likely to retain antibodies to the causative drug longer. People with drug allergies should be taught about avoiding the drug and should carry identification or an alert bracelet. Charts should always be appropriately marked.

Treatment

• Drug discontinuation

• Supportive treatment (eg, antihistamines, corticosteroids, epinephrine)

• Sometimes desensitization

Treatment is stopping the implicated drug; most symptoms and signs clear within a few days after the drug is stopped.

Symptomatic and supportive treatment for acute reactions may include antihistamines for pruritus, NSAIDs for arthralgias, corticosteroids for severe reactions (eg, exfoliative dermatitis, bronchospasm), and epinephrine for anaphylaxis. Conditions such as drug fever, a nonpruritic skin rash, or mild organ system reactions require no treatment (for treatment of specific clinical reactions, see elsewhere in THE MANUAL).

Desensitization: Rapid desensitization may be necessary if sensitivity has been established and if treatment is essential and no alternative exists. If possible, desensitization should be done in collaboration with an allergist. The procedure should not be attempted in patients who have had Stevens-Johnson syndrome. Whenever desensitization is used, O_2, epinephrine, and resuscitation equipment must be available for prompt treatment of anaphylaxis.

Desensitization is based on incremental dosing of the antigen every 30 min, beginning with a minute dose to induce subclinical anaphylaxis before exposure to therapeutic doses. This procedure depends on constant presence of drug in the serum and so must not be interrupted; desensitization is immediately followed by full therapeutic doses. Hypersensitivity typically returns 24 to 48 h after treatment is stopped. Minor reactions (eg, itching, rash) are common during desensitization.

For penicillin, oral or IV regimens can be used; sc or IM regimens are not recommended. If only the intradermal skin test is positive, 100 units (or µg)/mL IV in a 50-mL bag (5000 units total) should be given very slowly at first. If no symptoms appear, flow rate can be increased gradually until the bag is empty, after 20 to 30 min. The procedure is then repeated with concentrations of 1,000 units/mL and 10,000 units/mL, followed by the full therapeutic dose. If any allergic symptoms develop, flow rate should be slowed, and patients are given appropriate drug treatment (see above). If the prick test for penicillin was positive or patients have had a severe anaphylactic reaction, the starting dose should be lower.

Oral penicillin desensitization begins with 100 units (or µg); doses are doubled every 15 min up to 400,000 units (dose 13). Then, the drug is given parenterally, and if symptoms occur, they are relieved with appropriate anti-anaphylactic drugs.

For allergies to trimethoprim-sulfamethoxazole and vancomycin, regimens similar to those for penicillin can be used.

If a skin test to xenogeneic serum is positive, risk of anaphylaxis is high. If serum treatment is essential, desensitization must precede it. Skin tests, using weak concentrations prepared by serial dilution, are used to determine the appropriate starting dose for desensitization (ie, the concentration that produces a negative or only a weak reaction). 0.1 mL of this solution is injected sc or slowly IV; the IV route, although not standard, gives the clinician control over concentration and rate of delivery. If no reaction occurs in 15 min, the dose is doubled every 15 min until 1 mL of undiluted serum is given. This dose is repeated IM, and if no reaction occurs in another 15 min, the full dose can be given. If a reaction occurs, treatment may still be possible; the dose is reduced, an antihistamine is given as for acute urticaria, and the dose is then increased by smaller increments.

Mastocytosis

Mastocytosis is mast cell infiltration of skin or other tissues and organs. Symptoms result mainly from mediator release and include pruritus, flushing, and dyspepsia due to gastric hypersecretion. Diagnosis is by skin or bone marrow biopsy or both. Treatment is with antihistamines and control of any underlying disorder.

Mastocytosis is a group of disorders characterized by proliferation of mast cells and infiltration of the skin, other organs, or both. Pathology results mainly from release of mast cell mediators, including histamine, heparin, leukotrienes, and various inflammatory cytokines. Histamine causes many symptoms, including gastric symptoms, but other mediators also contribute. Significant organ infiltration may cause organ dysfunction. Mediator release may be triggered by physical touch, exercise, alcohol, NSAIDs, opioids, insect stings, or foods.

Etiology in many patients involves an activating mutation (D816V) in the gene coding for the stem cell factor receptor c-kit, present on mast cells.

Classification

Mastocytosis may be cutaneous or systemic.

Cutaneous mastocytosis: This type typically occurs in children. Most patients present with urticaria pigmentosa, a local or diffusely distributed salmon or brown maculopapular skin rash caused by multiple small mast cell collections. Less common are diffuse cutaneous mastocytosis, which is skin infiltration without discrete lesions, and mastocytoma, which is a large (1 to 5 cm) solitary collection of mast cells.

Systemic mastocytosis: This type most commonly occurs in adults and is characterized by multifocal bone marrow lesions; it often involves other organs, most commonly the skin, lymph nodes, liver, spleen, or GI tract. Systemic mastocytosis is classified as

- Indolent mastocytosis, with no organ dysfunction and a good prognosis
- Mastocytosis associated with other hematologic disorders (eg, myeloproliferative disorders, myelodysplasia, lymphoma)
- Aggressive mastocytosis, characterized by impaired organ function
- Mast cell leukemia, with > 20% mast cells in bone marrow, no skin lesions, multiorgan failure, and a poor prognosis

Symptoms and Signs

Skin involvement is often pruritic. Stroking or rubbing skin lesions causes urticaria and erythema around the lesion (Darier's sign); this reaction differs from dermatographism, which involves normal skin.

Systemic symptoms can occur with any form. The most common is flushing; the most dramatic is anaphylactoid reaction with syncope and shock. Other symptoms include epigastric pain due to peptic ulcer disease, nausea, vomiting, chronic diarrhea, arthralgias, bone pain, and neuropsychiatric changes (eg, irritability, depression, mood lability). Hepatic and splenic infiltration may cause portal hypertension with resultant ascites.

Diagnosis

• Clinical evaluation

• Skin lesion biopsy and sometimes bone marrow biopsy

Diagnosis is suggested by clinical presentation. Diagnosis is confirmed by biopsy of skin lesions and sometimes of bone marrow. Multifocal, dense infiltrates of mast cells are present.

Tests may be done to rule out disorders that cause similar symptoms (anaphylaxis, pheochromocytoma, carcinoid syndrome, and Zollinger-Ellison syndrome). Serum gastrin level is useful to rule out Zollinger-Ellison syndrome in patients with ulcer symptoms; urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA) is measured to rule out carcinoid in patients with flushing.

If the diagnosis is uncertain, levels of mast cell mediators and their metabolites (eg, urinary *N*-methylhistamine and *N*-methylimidazole acetic acid) may be measured in plasma and urine; elevated levels support the diagnosis of mastocytosis. The level of tryptase (a marker of mast cell degranulation) is elevated in systemic mastocytosis but is typically normal in cutaneous mastocytosis. A bone scan, GI workup, and identification of the D816V *c-kit* mutation can also be helpful in cases where the diagnosis requires confirmation.

Treatment

• For cutaneous mastocytosis, H_1 blockers and possibly psoralen plus ultraviolet light or topical corticosteroids

• For systemic mastocytosis, H_1 and H_2 blockers and sometimes cromolyn

• For aggressive forms, interferon alfa-2b, corticosteroids, or splenectomy

Cutaneous mastocytosis: H_1 blockers are effective for symptoms. Children with cutaneous forms require no additional treatment because most cases resolve spontaneously. Adults with cutaneous forms may be treated with psoralen plus ultraviolet light or with topical corticosteroids once/day or bid. Mastocytoma usually involutes spontaneously and requires no treatment. Cutaneous forms rarely progress to systemic disease in children but may do so in adults.

Systemic mastocytosis: All patients should be treated with H_1 and H_2 blockers. Aspirin controls flushing but may enhance leukotriene production, thereby contributing to mast cell-related symptoms; it should not be given to children because Reye's syndrome is a risk. Cromolyn 200 mg po qid (100 mg qid for children 2 to 12 yr; not to exceed 40 mg/kg/day) may help by preventing mast cell degranulation. No treatment can reduce the number of tissue mast cells. Ketotifen 2 to 4 mg po bid is inconsistently effective.

In patients with an aggressive form, interferon alfa-2b 4 million units sc once/wk to a maximum of 3 million units/day induces regression of bone lesions. Corticosteroids (eg, prednisone 40 to 60 mg po once/day for 2 to 3 wk) may be required. Splenectomy may improve survival.

Cytotoxic drugs (eg, daunomycin, etoposide, 6-mercaptopurine) may be indicated for treatment of mast cell leukemia, but efficacy is unproved. Imatinib (a tyrosine kinase receptor inhibitor) may be useful in some patients but is ineffective in patients with the D816V *c-kit* mutation. Midostaurin (a 2nd-generation tyrosine kinase receptor inhibitor) is under study in such patients.

Chapter 128. Transplantation

Introduction

Transplants may be the patient's own tissue (autografts; eg, bone, bone marrow, and skin grafts), genetically identical (syngeneic) donor tissue (isografts), genetically dissimilar donor tissue (allografts, or homografts), or, rarely, grafts from a different species (xenografts, or heterografts). Transplanted tissue may be cells (as for hematopoietic stem cell [HSC], lymphocyte, and pancreatic islet cell transplants), parts or segments of an organ (as for hepatic or pulmonary lobar transplants and skin grafts), or entire organs (as for heart transplants).

Tissues may be grafted to an anatomically normal site (orthotopic; eg, heart transplants) or abnormal site (heterotopic; eg, a kidney transplanted into the iliac fossa). Almost always, transplantation is done to improve patient survival. However, some procedures (eg, hand, larynx, tongue, and facial transplantation) attempt to improve quality of life but jeopardize quantity of life and thus are controversial.

With rare exceptions, clinical transplantation uses allografts from living related, living unrelated, or deceased donors. Living donors are often used for kidney and HSC transplants and increasingly for segmental liver, pancreas, and lung transplants. Use of deceased-donor organs (from heart-beating or non-heart-beating donors) has helped reduce the disparity between organ demand and supply; however, demand still far exceeds supply, and the number of patients waiting for organ transplants continues to grow.

All allograft recipients are at risk of graft rejection; the recipient's immune system recognizes the graft as foreign and seeks to destroy it. Recipients of grafts containing immune cells are at risk of graft-vs-host disease. Risk of these complications is minimized by pretransplantation screening and immunosuppressive therapy during and after transplantation.

Organ distribution: Allocation depends on disease severity for some organs (liver, heart) and on disease severity, time on the waiting list, or both for others (kidney, lung, bowel). In the US and Puerto Rico, organs are allocated first among 12 geographic regions, then among local Organ Procurement Organizations. If no recipient in the first region is suitable, organs are reallocated to recipients in other regions.

Pretransplantation Screening

Before the risk and expense of transplantation are undertaken and scarce donor organs are committed, physicians screen potential recipients for medical and nonmedical factors that may affect the likelihood of success.

Tissue compatibility: In pretransplantation screening, recipients and donors are tested for human leukocyte antigen (HLA) and ABO antigens, and recipients are tested for presensitization to donor antigens. HLA tissue typing is most important for kidney and the most common types of HSC transplantation. Heart, liver, pancreas, and lung transplantation typically occurs quickly, often before HLA tissue typing can be completed, so the role of matching for these organs is less well established.

HLA tissue typing of peripheral blood or lymph node lymphocytes is used to match the most important known determinants of histocompatibility in the donor and recipient. More than 1250 alleles determine 6 HLA antigens (HLA-A, -B, -C, -DP, -DQ, -DR), so matching is a challenge; eg, in the US, only 2 of 6 antigens on average are matched in kidney donors and recipients. Matching of as many HLA antigens as possible significantly improves functional survival of grafts from living related kidney and HSC donors; HLA matching of grafts from unrelated donors also improves survival, although much less so because of multiple undetected histocompatibility differences. Better immunosuppressive therapy has expanded eligibility for transplantation; HLA mismatches no longer automatically disqualify patients for transplantation.

ABO compatibility and HLA compatibility are important for graft survival. ABO mismatches can precipitate hyperacute rejection of highly vascular grafts (eg, kidney, heart), which have ABO antigens on the

endothelial surfaces. Presensitization to HLA and ABO antigens results from prior blood transfusions, transplantations, or pregnancies and can be detected with serology tests or, more commonly, with a lymphocytotoxic test using the recipient's serum and donor's lymphocytes in the presence of complement. A positive cross-match indicates that the recipient's serum contains antibodies directed against ABO or class I HLA antigens in the donor; it is an absolute contraindication to transplantation, except possibly in infants (up to age 14 mo) who have not yet produced isohemagglutinins. High-dose IV immune globulin has been used to suppress HLA antibodies and facilitate transplantation, but long-term outcomes are unknown. A negative cross-match does not guarantee safety; when ABO antigens are compatible but not identical (eg, donor O and recipient A, B, or AB), hemolysis is a potential complication due to antibody production by transplanted (passenger) donor lymphocytes.

Although matching for HLA and ABO antigens generally improves graft survival, nonwhite patients are disadvantaged because they may have different HLA polymorphisms from white donors, a higher rate of presensitization to HLA antigens, and a higher incidence of blood types O and B.

Infection: Donor and recipient exposure to common infectious pathogens and active infections must be detected before transplantation to minimize risk of transmitting infection from the donor and risk of worsening or reactivating existing infection in the recipient (due to use of immunosuppressants). This screening usually includes the history; serologic tests for cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus (HSV), varicellazoster virus (VZV), hepatitis B and C viruses, HIV, and West Nile virus (if exposure is suspected); and tuberculin skin testing. Positive findings may require post-transplantation antiviral treatment (eg, for CMV infection or hepatitis B) or contraindicate transplantation (eg, if HIV with AIDS is detected).

Contraindications to transplantation: Absolute contraindications to transplantation include active infection and cancer (except hepatocellular carcinoma confined to the liver and certain neuroendocrine tumors).

Relative contraindications include age > 65, poor functional or nutritional status (including severe obesity), HIV infection, and multiorgan insufficiency. Psychologic and social factors also play a role in success of transplantation. For example, people who abuse drugs or who are psychologically unstable are less likely to firmly adhere to the necessary lifelong regimen of treatments and follow-up visits. Eligibility decisions for patients with relative contraindications differ by medical center. Immunosuppressants are safe and effective for HIV-positive transplant recipients.

Immunosuppression

Immunosuppressants control graft rejection and are primarily responsible for the success of transplantation. However, they suppress all immune responses and contribute to many post-transplantation complications, including death due to overwhelming infection. Except when HLA-identical transplants are used, immunosuppressants must usually be continued long after transplantation, but initially high doses can be reduced a few weeks after the procedure, and low doses can be continued indefinitely unless rejection occurs.

Corticosteroids: A high dose is usually given at the time of transplantation, then is reduced gradually to a maintenance dose, which is given indefinitely. Several months after transplantation, corticosteroids can be given on alternate days; this regimen helps prevent growth restriction in children. If rejection occurs, high doses are reinstituted.

Calcineurin inhibitors (CNIs): These drugs (cyclosporine, tacrolimus) block T-cell transcription processes required for production of cytokines, thereby selectively inhibiting T-cell proliferation and activation.

Cyclosporine is the most commonly used drug in heart and lung transplantation. It can be given alone but is usually given with other drugs (eg, azathioprine, prednisone), so that lower, less toxic doses can be used. The initial dose is reduced to a maintenance dose soon after transplantation. The drug is metabolized by the cytochrome P-450 3A enzyme, and blood levels are affected by many other drugs. The most serious adverse effect is nephrotoxicity; cyclosporine causes vasoconstriction of afferent

(preglomerular) arterioles, leading to glomerular apparatus damage, refractory glomerular hypoperfusion, and, eventually, chronic renal failure. Also, B-cell lymphomas and polyclonal B-cell lymphoproliferation occur more often in patients receiving high doses of cyclosporine or combinations of cyclosporine and other immunosuppressants directed at T cells, possibly because of an association with EBV. Other adverse effects include diabetes, hepatotoxicity, refractory hypertension, increased incidence of other tumors, and less serious effects (eg, gum hypertrophy, hirsutism). Serum cyclosporine levels do not correlate with effectiveness or toxicity.

Tacrolimus is the most commonly used drug in kidney, liver, pancreas, and small-bowel transplantation. Tacrolimus may be started at the time of transplantation or days after the procedure. Dosing should be guided by blood levels, which are influenced by the same drug interactions as for cyclosporine. Tacrolimus may be useful when cyclosporine is ineffective or has intolerable adverse effects. Adverse effects of tacrolimus are similar to those of cyclosporine except tacrolimus is more prone to induce diabetes; gum hypertrophy and hirsutism are less common. Lymphoproliferative disorders seem to occur more often in patients taking tacrolimus, even weeks after transplantation. If they occur, tacrolimus should be stopped and cyclosporine or another immunosuppressive drug substituted.

Purine metabolism inhibitors: Examples are azathioprine and mycophenolate mofetil.

Azathioprine, an antimetabolite, is usually started at the time of transplantation. Most patients tolerate it indefinitely. The most serious adverse effects are bone marrow depression and, rarely, hepatitis. Azathioprine is often used with low doses of cyclosporine.

Mycophenolate mofetil (MMF), a prodrug metabolized to mycophenolic acid, reversibly inhibits inosine monophosphate dehydrogenase, an enzyme in the guanine nucleotide pathway that is rate-limiting in lymphocyte proliferation. MMF is given with cyclosporine (or tacrolimus) and corticosteroids to patients with a kidney, heart, or liver transplant. The most common adverse effects are leukopenia, nausea, vomiting, and diarrhea.

Rapamycins: These drugs (sirolimus, everolimus) block a key regulatory kinase in lymphocytes, resulting in arrest of the cell cycle and in inhibition of lymphocyte response to cytokine stimulation.

Sirolimus is typically given with cyclosporine and corticosteroids and may be useful for patients with renal insufficiency. Adverse effects include hyperlipidemia, impaired wound healing, and bone marrow depression with leukopenia, thrombocytopenia, and anemia.

Everolimus is typically used to prevent heart transplant rejection; adverse effects are similar to those of sirolimus.

Immunosuppressive Igs: Examples are antilymphocyte globulin (ALG) and antithymocyte globulin (ATG). Both are fractions of animal antisera directed against human cells: lymphocytes (ALG) or thymus cells (ATG). ALG and ATG suppress cellular immunity while preserving humoral immunity. They are used with other immunosuppressants to allow those drugs to be used in lower, less toxic doses. Use of ALG or ATG to control acute episodes of rejection improves graft survival rates; use at the time of transplantation may decrease rejection incidence and allow CNIs to be started later, thereby reducing toxicity. Use of highly purified serum fractions has greatly reduced incidence of adverse effects (eg, anaphylaxis, serum sickness, antigen-antibody-induced glomerulonephritis).

Monoclonal antibodies (mAbs): mAbs directed against T cells provide a higher concentration of anti-T-cell antibodies and fewer irrelevant serum proteins than do ALG and ATG. OKT3 inhibits T-cell receptor (TCR)-antigen binding, resulting in immunosuppression. OKT3 is used primarily to control episodes of acute rejection; it may also be used at the time of transplantation to reduce incidence or delay onset of rejection episodes. However, benefits of prophylactic use must be weighed against adverse effects, which include severe CMV infection and development of neutralizing antibodies; these effects preclude using OKT3 for an actual rejection episode. With first use, OKT3 binds to the TCR-CD3 complex, activating the cell and triggering release of cytokines, which cause a syndrome of fevers, rigors, myalgias, arthralgias, nausea, vomiting, and diarrhea. Pretreatment with corticosteroids, antipyretics, and antihistamines can ameliorate these symptoms. The first-dose reaction less commonly includes chest

pain, dyspnea, and wheezing, possibly due to complement activation. Repeated use is associated with increased incidence of EBV-induced B-cell lymphoproliferative disorders. Rarely, aseptic meningitis and hemolytic uremic syndrome occur.

Anti-IL-2 receptor monoclonal antibodies inhibit T-cell proliferation by blocking the effect of IL-2, secreted by activated T cells. Basiliximab and daclizumab, 2 humanized anti-IL-2 receptor antibodies, are increasingly being used to treat acute rejection of kidney, liver, and small-bowel transplants; they are also used as adjunct immunosuppressive therapy at the time of transplantation. The only adverse effect reported is anaphylaxis. Also, experience with IL-2 receptor antibodies is limited, and an increased risk of lymphoproliferative disorders cannot be excluded.

Irradiation: Irradiation of a graft, local recipient tissues, or both can be used to treat kidney transplant rejection episodes when other treatment (eg, corticosteroids and ATG) is ineffective. Total lymphatic irradiation is experimental but appears to safely suppress cellular immunity, at first by stimulation of suppressor T cells and later possibly by clonal deletion of specific antigen-reactive cells.

Future therapies: Protocols and agents to induce graft antigen-specific tolerance without suppressing other immune responses are being sought. Two strategies are promising:

- Blockade of T-cell costimulatory pathways using a cytotoxic T lymphocyte-associated antigen 4 (CTLA-4)-IgG1 fusion protein

- Induction of chimerism (coexistence of donor and recipient immune cells in which graft tissue is recognized as self) using nonmyeloablative pretransplantation treatment (eg, with cyclophosphamide, thymic irradiation, ATG, and cyclosporine) to induce transient T-cell depletion, engraftment of donor HSCs, and subsequent tolerance of solid organ transplants from the same donor

Post-transplantation Complications

Complications include the following:

- Rejection

- Infection

- Renal insufficiency

- Cancer

Rejection: Rejection of solid organs may be hyperacute, accelerated, acute, or chronic (late). These categories overlap somewhat in timing but can be distinguished histopathologically. Symptoms vary by organ (see
Table 128-1).

Hyperacute rejection occurs within 48 h of transplantation and is caused by preexisting complement-fixing antibodies to graft antigens (presensitization). It has become rare (1%) as pretransplantation screening has improved. Hyperacute rejection is characterized by small-vessel thrombosis and graft infarction. No treatment is effective except graft removal.

Accelerated rejection occurs 3 to 5 days after transplantation and is caused by preexisting noncomplement-fixing antibodies to graft antigens. Accelerated rejection is also rare. It is characterized histopathologically by cellular infiltrate with or without vascular changes. Treatment is with high-dose pulse corticosteroids or, if vascular changes occur, antilymphocyte preparations. Plasmapheresis, which may clear circulating antibodies more rapidly, has been used.

Acute rejection is graft destruction after transplantation and is caused by a T cell-mediated delayed hypersensitivity reaction to allograft histocompatibility antigens. It accounts for about one half of all rejection episodes that occur within 10 yr. Acute rejection is characterized by mononuclear cellular

infiltration, with varying degrees of hemorrhage, edema, and necrosis. Vascular integrity is usually maintained, although vascular endothelium appears to be a primary target. Acute rejection is often reversed by intensifying immunosuppressive therapy (eg, with pulse corticosteroids, ALG, or both). After rejection

[**Table 128-1.** Signs of Transplant Rejection by Category]

reversal, severely damaged parts of the graft heal by fibrosis, the remainder of the graft functions normally, immunosuppressant doses can be reduced to very low levels, and the allograft can survive for long periods.

Chronic rejection is graft dysfunction, often without fever, typically occurring months to years after transplantation but sometimes within weeks. Causes are multiple and include early antibody-mediated rejection, periprocedural ischemia and reperfusion injury, drug toxicity, infection, and vascular factors (eg, hypertension, hyperlipidemia). Chronic rejection accounts for most of the other one half of all rejection episodes. Proliferation of neointima consisting of smooth muscle cells and extracellular matrix (transplantation atherosclerosis) gradually and eventually occludes vessel lumina, resulting in patchy ischemia and fibrosis of the graft. Chronic rejection progresses insidiously despite immunosuppressive therapy; no established treatments exist.

Infection: Immunosuppressants, secondary immunodeficiencies that accompany organ failure, and surgery make transplant patients more vulnerable to infections. Rarely, a transplanted organ is the source of infection (eg, CMV).

The most common sign is fever, often without localizing signs. Fever can also be a symptom of acute rejection but is usually accompanied by signs of graft dysfunction. If these signs are absent, the approach is similar to that for other FUO (see p. 1157); timing of symptoms and signs after transplantation helps narrow the differential diagnosis.

In the first month after transplantation, most infections are caused by the same hospital-acquired bacteria and fungi that infect other surgical patients (eg, *Pseudomonas* sp causing pneumonia, gram-positive bacteria causing wound infections). The greatest concern with early infection is that organisms can infect a graft or its vascular supply at suture sites, causing mycotic aneurysms or dehiscence.

Opportunistic infections occur 1 to 6 mo after transplantation (for treatment, see elsewhere in The Manual). Infections may be bacterial (eg, listeriosis, nocardiosis), viral (eg, due to CMV, EBV, VZV, or hepatitis B or C virus), fungal (eg, aspergillosis, cryptococcosis, *Pneumocystis jirovecii* infection), or parasitic (eg, strongyloidiasis, toxoplasmosis, trypanosomiasis, leishmaniasis).

Risk of infection returns to baseline for about 80% of patients after 6 mo. About 10% develop complications of early infections, such as viral infection of the graft, metastatic infection (eg, CMV retinitis, colitis), or virus-induced cancers (eg, hepatitis and hepatocellular carcinoma, human papillomavirus and basal cell carcinoma). Others develop chronic rejection, require high doses of immunosuppressants (5 to 10%), and remain at high risk of opportunistic infections indefinitely.

After transplantation, most patients are given antimicrobials to reduce risk of infection. Choice of drug depends on individual risk and type of transplantation; regimens include trimethoprim/sulfamethoxazole 80/400 mg po once/day for 4 to 12 mo to prevent *P. jirovecii* infection or to prevent UTIs in kidney transplant patients. Neutropenic patients are sometimes given quinolone antibiotics (eg, levofloxacin 500 mg po or IV once/day) to prevent infection with gram-negative organisms. Inactivated vaccines can be safely given post-transplantation; risks due to live-attenuated vaccines must be balanced against their potential benefits, especially for patients taking low doses of immunosuppressants.

Renal disorders: GFR decreases 30 to 50% during the first 6 mo after solid organ transplantation in 15 to 20% of patients. They usually also develop hypertension. Incidence is greatest for recipients of small-bowel transplants (21%) and least for recipients of heart-lung transplants (7%). Nephrotoxic and diabetogenic effects of CNIs are the most important contributor, but periprocedural renal insults, pretransplantation renal insufficiency, hepatitis C infection, and use of other nephrotoxic drugs also

contribute. After the initial decrease, GFR typically stabilizes or decreases more slowly; nonetheless, mortality risk quadruples unless subsequent kidney transplantation is done. Renal insufficiency after transplantation may be prevented by early weaning from CNIs, but a safe minimum dose has not been determined.

Cancer: Long-term immunosuppression increases incidence of virus-induced cancer, especially squamous and basal cell carcinoma, lymphoproliferative disorders (mainly B-cell non-Hodgkin lymphoma), anogenital (including cervical) cancer, and Kaposi's sarcoma. Treatment is similar to that of cancer in nonimmunosuppressed patients; reduction or interruption of immunosuppression is not usually required for low-grade tumors but is recommended for more aggressive tumors and lymphomas.

Transfusion of partially HLA-matched cytotoxic T cells is under study as a possible treatment for some forms of lymphoproliferative disorders.

Other complications: Immunosuppressants (especially corticosteroids and CNIs) increase bone resorption and risk of osteoporosis for patients who are at risk before transplantation (eg, because of reduced physical activity, tobacco and alcohol use, or a preexisting renal disorder). Although not routine, use of vitamin D, bisphosphonates, or other antiresorptive drugs after transplantation may play a role in prevention.

Failure to grow, primarily as a consequence of chronic corticosteroid use, is a concern in children. Growth failure can be mitigated by tapering corticosteroids to the minimum dose that does not lead to graft rejection.

Systemic atherosclerosis can result from hyperlipidemia due to use of CNIs and corticosteroids; it typically occurs in kidney transplant recipients > 15 yr post-transplantation.

Graft vs host disease (GVHD) occurs when donor T cells react against recipient's self-antigens. GVHD primarily affects hematopoietic stem cell recipients (see p. 1132) but may also affect liver and small-bowel transplant recipients.

Heart Transplantation

Heart transplantation is an option for patients who have end-stage heart failure, coronary artery disease (CAD), arrhythmias, hypertrophic cardiomyopathy, or congenital heart disease and who remain at risk of death and have intolerable symptoms despite optimal use of drugs and medical devices. Transplantation may also be indicated for patients who cannot be weaned from temporary cardiac-assist devices after MI or nontransplant cardiac surgery and for patients with cardiac sequelae of a lung disorder requiring lung transplantation. The only absolute contraindication is pulmonary hypertension; relative contraindications include organ insufficiency (eg, pulmonary, renal, hepatic) and local or systemic infiltrative disorders (eg, cardiac sarcoma, amyloidosis).

All donated hearts come from brain-dead donors, who must be < 60 and have normal cardiac and pulmonary function and no history of CAD or other heart disorders. Donor and recipient must have compatible ABO blood type and heart size. About 25% of eligible recipients die before a donor organ becomes available. Left ventricular assist devices and artificial hearts provide interim hemodynamic support for patients waiting for a transplant. However, if left in place too long, these devices put the recipient at high risk of sepsis, device failure, and thromboembolism.

Procedure

Donor hearts are preserved by hypothermic storage. They must be transplanted within 4 to 6 h. The recipient is placed on a bypass pump, and the recipient heart is removed, preserving the posterior right atrial wall in situ. The donor heart is then transplanted orthotopically with aortic, pulmonary artery, and pulmonary vein anastomoses; a single anastomosis joins the retained posterior atrial wall to that of the donor organ.

Immunosuppressive regimens vary but are similar to those for kidney or liver transplantation (eg, anti-IL-2

receptor monoclonal antibodies, a calcineurin inhibitor, corticosteroids). About 50 to 80% of patients have at least 1 episode of rejection (average 2 to 3); most patients are asymptomatic, but about 5% develop left ventricle dysfunction or atrial arrhythmias. Incidence of acute rejection peaks at 1 mo, decreases over the next 5 mo, and levels off by 1 yr. Risk factors for rejection include younger age, female recipient, female or black donor, and HLA mismatching. Cytomegalovirus (CMV) infection may also influence risk.

Because graft damage can be irreversible and catastrophic, surveillance endomyocardial biopsy is usually done once/yr; degree and distribution of mononuclear cell infiltrate and presence of myocyte injury in specimens is determined. Differential diagnosis includes perioperative ischemia, CMV infection, and idiopathic B-cell infiltration (Quilty lesions). Mild rejection (grade 1) without detectable clinical sequelae requires no treatment; moderate or severe rejection (grades 2 to 4) or mild rejection with clinical sequelae is treated with corticosteroids and antithymocyte globulin or OKT3 as needed.

The main complication is cardiac allograft vasculopathy, a form of atherosclerosis that diffusely narrows or obliterates vessel lumina (in 25% of patients). Its cause is probably multifactorial and relates to donor age, cold and reperfusion ischemia, dyslipidemia, immunosuppressants, chronic rejection, and viral infection (adenovirus in children, CMV in adults). For early detection, surveillance stress testing or coronary angiography with or without intravascular ultrasonography is often done at the time of endomyocardial biopsy. Treatment is aggressive lipid lowering (see p. 896) and diltiazem; everolimus 1.5 mg po bid may be preventive.

Prognosis

Survival rates at 1 yr are 85%, and annual mortality thereafter is about 4%. Pretransplantation predictors of 1-yr mortality include need for preoperative ventilation or left ventricular assist devices, cachexia, female recipient or donor, and diagnoses other than heart failure or CAD. Post-transplantation predictors include elevated C-reactive protein and troponin levels.

Cause of death within 1 yr is most often acute rejection and infection; cause after 1 yr is most often cardiac allograft vasculopathy or a lymphoproliferative disorder. Prognosis of recipients alive at > 1 yr is excellent; exercise capacity remains below normal but is sufficient for daily activities and may increase over time with sympathetic reinnervation. More than 95% of patients reach New York Heart Association class I cardiac status, and > 70% return to full-time employment.

Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell (HSC) transplantation is a rapidly evolving technique that offers a potential cure for hematologic cancers (leukemias, lymphomas, myeloma) and other hematologic disorders (eg, primary immunodeficiency, aplastic anemia, myelodysplasia). HSC transplantation may be autologous or allogeneic; bone marrow, peripheral blood, or umbilical cord stem cells may be used. Peripheral blood has largely replaced bone marrow as a source of stem cells, especially in autologous HSC transplantation, because stem cell harvest is easier and neutrophil and platelet counts recover faster. Umbilical cord HSC transplantation has been restricted mainly to children because the number of stem cells is low.

There are no contraindications to autologous HSC transplantation. Contraindications to allogeneic HSC transplantation are relative and include age > 50, previous HSC transplantation, and significant comorbidities. Allogeneic HSC transplantation is limited mainly by lack of histocompatible donors. An HLA-identical sibling donor is ideal, followed by an HLA-matched sibling donor. Because only one fourth of patients have such a sibling donor, mismatched related or matched unrelated donors (identified through international registries) are often used. However, long-term disease-free survival rates may be lower than those with HLA-identical sibling donors. The technique for umbilical cord HSC transplantation is still being defined, but HLA-matching is probably unimportant.

Procedure

For bone marrow stem cell harvest, 700 to 1500 mL (maximum 15 mL/kg) of marrow is aspirated from the donor's posterior iliac crests; local or general anesthesia is used. For peripheral blood harvest, the donor is treated with recombinant growth factors (granulocyte colony-stimulating factor or granulocyte-

macrophage colony-stimulating factor) to stimulate proliferation and mobilization of stem cells, with standard phlebotomy 4 to 6 days afterward. Fluorescence-activated cell sorting is used to identify and separate stem cells from other cells.

Stem cells are then infused over 1 to 2 h through a large-bore central venous catheter. In HSC transplantation for cancer, the recipient first is given a conditioning regimen (eg, cyclophosphamide 60 mg/kg IV once/day for 2 days with total body irradiation, busulfan 1 mg/kg po qid for 4 days plus cyclophosphamide without total body irradiation) to induce remission and suppress the immune system so that the graft can be accepted. Similar regimens are used for allogeneic HSC transplantation, even when cancer is not the indication, to reduce incidence of rejection and relapse, but not for autologous HSC transplantation. Nonmyeloablative conditioning regimens may reduce morbidity and mortality risks and may be useful for elderly patients, patients with comorbidities, and patients susceptible to a graft-vs-tumor effect (eg, those with multiple myeloma).

After transplantation, recipients are given colony-stimulating factors to shorten duration of post-transplantation leukopenia, prophylactic anti-infective drugs (see p. 1130), and, in allogeneic HSC transplantation, up to 6 mo of prophylactic immunosuppressants (typically methotrexate and cyclosporine) to prevent donor T cells from reacting against recipient major histocompatibility complex molecules (graft-vs-host disease [GVHD]). Broad-spectrum antibiotics are usually withheld unless fever develops. Engraftment typically occurs 10 to 20 days after HSC transplantation (earlier with peripheral blood stem cells) and is defined by an absolute neutrophil count > 500 × 10^6/L.

Major **early complications** (< 100 days) include

• Failure to engraft

• Rejection

• Acute GVHD

Failure to engraft and rejection affect < 5% of patients and manifest as persistent pancytopenia or irreversible decline in blood counts. Treatment is corticosteroids for several weeks.

Acute GVHD occurs in recipients of allogeneic HSC transplants, 40% of HLA-matched sibling graft recipients, and 80% of unrelated donor graft recipients. It causes fever, rash, hepatitis with hyperbilirubinemia, vomiting, diarrhea, abdominal pain (which may progress to ileus), and weight loss. Risk factors include HLA and sex mismatching; unrelated donor; older age of recipient, donor, or both; donor presensitization; and inadequate GVHD prophylaxis. Diagnosis is obvious by history and physical examination; treatment is methylprednisolone 2 mg/kg IV once/day, increased to 10 mg/kg if there is no response within 5 days.

Major **later complications** include

• Chronic GVHD

• Disease relapse

Chronic GVHD may occur by itself, develop from acute GVHD, or occur after resolution of acute GVHD. It typically occurs 4 to 7 mo after HSC transplantation (range 2 mo to 2 yr). Chronic GVHD occurs in recipients of allogeneic HSC transplants, about 35 to 50% of HLA-matched sibling graft recipients, and 60 to 70% of unrelated donor graft recipients. It affects primarily the skin (eg, lichenoid rash, scleroderma) and mucous membranes (eg, keratoconjunctivitis sicca, periodontitis, orogenital lichenoid reactions), but it also affects the GI tract and liver. Immunodeficiency is a primary feature; bronchiolitis obliterans similar to that after lung transplantation can also develop. Ultimately, 20 to 40% die of GVHD; mortality rate is higher with more severe reactions. Treatment may not be necessary for skin and mucous membrane disease; treatment of more extensive disease is similar to that of acute GVHD. T-cell depletion of allogeneic donor grafts using monoclonal antibodies or mechanical separation reduces incidence and severity of GVHD but also eliminates a graft-vs-tumor effect that may enhance stem cell proliferation and

engraftment and reduce disease relapse rates. Relapse rates with autologous HSC transplantation are higher for this reason and because circulating tumor cells may be transplanted. Ex vivo tumor cell purging before autologous transplantation is under study.

In patients without chronic GVHD, all immunosuppression can be stopped 6 mo after HSC transplantation; thus, late complications are rare in these patients.

Prognosis

Prognosis varies by indication and procedure. Overall, disease relapse occurs in 40 to 75% of recipients of autologous HSC transplants and in 10 to 40% of recipients of allogeneic HSC transplants. Success (cancer-free bone marrow) rates are 30 to 40% for patients with relapsed, chemotherapy-sensitive lymphoma and 20 to 50% for patients with acute leukemia in remission; compared with chemotherapy alone, HSC transplantation improves survival of patients with multiple myeloma. Success rates are low for patients with more advanced disease or with responsive solid cancers (eg, breast cancer, germ cell tumors). Relapse rates are reduced in patients with GVHD, but overall mortality rates are increased if GVHD is severe. Intensive preparative regimens, effective GVHD prophylaxis, cyclosporine-based regimens, and improved supportive care (eg, antibiotics, herpesvirus and cytomegalovirus prophylaxis) have increased long-term disease-free survival after HSC transplantation.

Kidney Transplantation

Kidney transplantation is the most common type of solid organ transplantation; the primary indication is end-stage renal failure. Absolute contraindications include comorbidities that could compromise graft survival (eg, severe heart disorders, cancer), which can be detected via thorough screening. Relative contraindications include poorly controlled diabetes, which can lead to renal failure. Patients in their 60s may be transplant candidates if they are otherwise healthy and functionally independent with good social support, if they have a reasonably long life expectancy, and if transplantation is likely to substantially improve function and quality of life beyond simply freeing them from dialysis. Patients with type 1 diabetes may be candidates for simultaneous pancreas-kidney or pancreas-after-kidney transplantation.

More than one half of donated kidneys come from previously healthy, brain-dead people. About one third of these kidneys are marginal, with physiologic or procedure-related damage, but are used because demand is so great. The remaining donated kidneys come from living donors; because of limited supply, allografts from carefully selected living unrelated donors are being increasingly used. Living donors relinquish reserve renal capacity, may put themselves at risk of procedural and long-term morbidity, and may have psychologic conflicts about donation; therefore, they are evaluated for normal bilateral renal function, absence of systemic disease, histocompatibility, emotional stability, and ability to give informed consent. Hypertension, diabetes, and cancer (except possibly CNS tumors) usually preclude kidney donation from living donors.

Procedure

The donor kidney is removed during an open or laparoscopic procedure, perfused with cooling solutions containing relatively large concentrations of poorly permeating substances (eg, mannitol, hetastarch) and electrolyte concentrations approximating intracellular levels, then stored in an iced solution. Kidneys preserved this way usually function well if transplanted within 48 h. Although not commonly used, continuous pulsatile hypothermic perfusion with an oxygenated, plasma-based perfusate can extend ex vivo viability up to 72 h.

Dialysis may be required before transplantation to ensure a relatively normal metabolic state, but living-donor allografts appear to survive better in recipients who have not begun long-term dialysis before transplantation. Nephrectomy is usually not required unless native kidneys are infected. Whether transfusions are useful for anemic patients anticipating an allograft is unclear; transfusions can sensitize patients to alloantigens, but allografts may survive better in recipients who receive transfusions but do not become sensitized, possibly because transfusions induce some form of tolerance.

The transplanted kidney is usually placed in the iliac fossa. Renal vessels are anastomosed to the iliac

vessels, and the donor ureter is implanted into the bladder or anastomosed to the recipient ureter. Vesicoureteral reflux occurs in about 30% of recipients but is usually harmless.

Immunosuppressive regimens vary. Commonly, calcineurin inhibitors are begun immediately after transplantation in doses titrated to minimize toxicity and rejection while maintaining trough blood levels > 200 ng/mL. On the day of transplantation, IV or oral corticosteroids are also given; dose is tapered over the following 12 wk.

Despite use of immunosuppressants, about 20% of recipients have one or more rejection episodes within the first year after transplantation. Most episodes are probably insignificant, subclinical, and therefore never detected; however, they contribute to long-term insufficiency, graft failure, or both. Signs of rejection vary by type (see Table 128-1).

Rejection can be diagnosed by percutaneous needle biopsy if the diagnosis is unclear clinically. Biopsy may also help distinguish antibody-mediated from T-cell-mediated rejection and identify other common causes of graft insufficiency or failure (eg, calcineurin inhibitor toxicity, diabetic or hypertensive nephropathy, polyomavirus type 1 infection). Advanced tests that may improve accuracy of rejection diagnosis include measurement of urinary mRNA-encoding mediators of rejection and gene expression profiling of biopsy samples using DNA microarrays.

Chronic allograft nephropathy refers to graft insufficiency or failure ≥ 3 mo after transplantation. Most cases are attributable to one or more of the above causes. Some experts believe the term should be reserved to describe graft insufficiency or failure when biopsy shows chronic interstitial fibrosis and tubular atrophy not attributable to any other cause.

Intensified immunosuppressive therapy (eg, with high-dose pulse corticosteroids or antilymphocyte globulin) usually reverses accelerated or acute rejection. If immunosuppressants are ineffective, dose is tapered and hemodialysis is resumed until a subsequent transplant is available. Nephrectomy of the transplanted kidney is necessary if hematuria, graft tenderness, or fever develops after immunosuppressants are stopped.

Prognosis

Most rejection episodes and other complications occur within 3 to 4 mo after transplantation; most patients then return to more normal health and activity but must take maintenance doses of immunosuppressants indefinitely.

At 1 yr, survival rates with living-donor grafts are 98% for patients and 94% for grafts; rates with deceased-donor grafts are 94% and 88%, respectively. Subsequent annual graft loss rates are 3 to 5% with a living-donor graft and 5 to 8% with a deceased-donor graft.

Among patients whose graft survives the first year, one half die of other causes with the graft functioning normally; one half develop chronic allograft nephropathy with the graft malfunctioning in 1 to 5 yr. Rates of late failure are higher for blacks than for whites.

Doppler ultrasonographic measurement of peak systolic and minimal end-diastolic flow in renal segmental arteries ≥ 3 mo after transplantation may help assess prognosis, but the gold standard remains serial determination of serum creatinine.

Liver Transplantation

Liver transplantation is the 2nd most common type of solid organ transplantation. Indications include cirrhosis (70% of US transplants, 60 to 70% of which are attributed to hepatitis C); fulminant hepatic necrosis (about 8%); hepatocellular carcinoma (about 7%); biliary atresia and metabolic disorders, primarily in children (about 3% each); and other cholestatic (eg, primary sclerosing cholangitis) and noncholestatic (eg, autoimmune hepatitis) disorders (about 8%). For patients with hepatocellular carcinoma, transplantation is indicated for 1 tumor < 5 cm or up to 3 tumors < 3 cm (Milan criteria) and for some fibrolamellar types. For patients with liver metastases, transplantation is indicated only for

neuroendocrine tumors without extrahepatic growth after removal of the primary tumor.

Absolute contraindications are elevated intracranial pressure (> 40 mm Hg) or low cerebral perfusion pressure (< 60 mm Hg) in patients with fulminant hepatic necrosis, severe pulmonary hypertension (mean pulmonary arterial pressure > 50 mm Hg), sepsis, and advanced or metastatic hepatocellular carcinoma; all of these conditions lead to poor outcomes during or after transplantation.

Nearly all donated livers come from size-and ABO-matched deceased, heart-beating donors. Annually, about 500 come from living donors, who can live without their right lobe (in adult-to-adult transplantation) or the lateral segment of their left lobe (in adult-to-child transplantation). Advantages of living donation for the recipient include shorter waiting times, shorter cold ischemic times for explanted organs, and the ability to schedule transplantation to optimize the patient's condition. Disadvantages to the donor include mortality risk of 1/300 to 400 (compared with 1/3300 in living-donor kidney transplantation) and complications (especially bile leakage) in up to one fourth, usually when resection is lobar (not segmental). Living donors are also at risk of psychologic coercion. A few livers come from deceased, non-heart-beating donors.

Donor (deceased or living) risk factors for graft failure in the recipient include age > 50; hepatic steatosis; elevated liver enzymes, bilirubin, or both; prolonged stay in ICU; hypotension requiring vasopressors; and hypernatremia. Transplants from female donors to male recipients may also increase risk. But because imbalance between supply and demand is greatest for liver transplants (and is growing because prevalence of hepatitis-induced cirrhosis is increasing), livers from donors > 50 and with short cold ischemia times, those with fatty infiltration, and those with viral hepatitis (for transplantation into recipients with viral hepatitis-induced cirrhosis) are increasingly being used.

Additional techniques to increase supply include split liver transplantation, in which deceased-donor livers are divided into right and left lobes or right lobe and left lateral segment (done in or ex situ) and given to 2 recipients, and domino transplantation, rarely indicated, in which a deceased-donor liver is given to a recipient with an infiltrative disease (eg, amyloidosis), and the explanted diseased liver is given to an elderly recipient who can benefit from the diseased liver but is not expected to live long enough to experience adverse effects of transplant dysfunction.

Despite these innovations, many patients die waiting for transplants. Liver-assist devices (extracorporeal perfusion of cultured hepatocyte suspensions or immortalized hepatoma cell lines) are used in some centers to keep patients alive until a liver is available or acute dysfunction resolves. For distribution of available organs, patients on the national waitlist are given a prognostic score derived from creatinine, bilirubin, and INR measurements (for adults) or from age and serum albumin, bilirubin, INR, and growth failure measurements (for children). For patients with hepatocellular carcinoma, the score incorporates tumor size and waiting time (increasing with each). Patients with higher scores are more likely to die and are given higher priority for organs from ABO- and weight-matched donors.

Procedure

Deceased-donor livers are removed after exploratory laparotomy confirms absence of intra-abdominal disease that would preclude transplantation. Living donors undergo lobar or segmental resection. Explanted livers are perfused and stored in a cold preservation solution for up to 24 h before transplantation; incidence of graft nonfunction and ischemic-type biliary injury increases with prolonged storage.

Recipient hepatectomy is the most demanding part of the procedure because it is often done in patients with portal hypertension and coagulation defects. Intraoperative blood loss can total > 100 units in rare cases, but use of a cell saver machine and autotransfusion devices reduce allogeneic transfusion requirements to an average of 5 to 10 units. After hepatectomy, the suprahepatic vena cava of the donor graft is anastomosed to the recipient's vena cava in an end-to-side fashion ("piggy-back" technique). Donor and recipient portal veins, hepatic arteries, and bile ducts are then anastomosed. With this technique, a bypass pump is not needed to carry portal venous blood to the systemic venous circuit. Heterotopic placement of the liver provides an auxiliary liver and obviates several technical difficulties, but outcomes have been discouraging, and this technique is still experimental.

Immunosuppressive regimens vary. Commonly, anti-IL-2 receptor monoclonal antibodies are given on the day of transplantation, with a calcineurin inhibitor (cyclosporine or tacrolimus), mycophenolate mofetil, and corticosteroids. Except in patients with autoimmune hepatitis, corticosteroids can be tapered within weeks and often stopped after 3 to 4 mo. Compared with other solid organ transplantation, liver transplantation requires the lowest doses of immunosuppressants.

Liver allografts are less aggressively rejected than other organ allografts for unknown reasons; hyperacute rejection occurs less frequently than expected in patients presensitized to HLA or ABO antigens, and immunosuppressants can often be tapered relatively quickly and eventually stopped. Most episodes of acute rejection are mild and self-limited, occur in the first 3 to 6 mo, and do not affect graft survival. Risk factors include younger recipient age, older donor age, greater HLA mismatching, longer cold ischemia times, and autoimmune disorders; worse nutritional status (eg, in alcoholism) appears protective.

Symptoms and signs of rejection depend on the type of rejection (see Table 128-1). Symptoms of acute rejection occur in about 50% of patients; symptoms of chronic rejection occur in < 2%.

Differential diagnosis of acute rejection includes viral hepatitis (eg, cytomegalovirus or Epstein-Barr virus infection; recurrent hepatitis B, C, or both), calcineurin inhibitor toxicity, and cholestasis. Rejection can be diagnosed by percutaneous needle biopsy if the diagnosis is unclear clinically. Suspected rejection is treated with IV corticosteroids; antithymocyte globulin and OKT3 are options when corticosteroids are ineffective (in 10 to 20%). Retransplantation is tried when rejection is refractory to immunosuppressants.

Immunosuppression contributes to recurrence of viral hepatitis in patients who had viral hepatitis-induced cirrhosis before transplantation. Hepatitis C recurs in nearly all patients; usually, viremia and infection are clinically silent but may cause active hepatitis and cirrhosis. Risk factors for clinically significant reinfection may be related to the recipient (older age, HLA type, hepatocellular carcinoma), donor (older age, fatty infiltration, prolonged ischemic time, living donor), virus (high viral load, genotype 1B, failure to respond to interferon), or postprocedural events (immunosuppressant doses, acute rejection treated with corticosteroids or OKT3, cytomegalovirus infection). Standard treatment (see p. 258) is only marginally effective. Hepatitis B recurs in all but has been successfully managed with hepatitis B immune globulin and lamivudine; co-infection with hepatitis D appears protective against recurrence.

Early (within 2 mo) complications of liver transplantation include primary nonfunction in 1 to 5%, biliary dysfunction (eg, ischemic anastomotic strictures, bile leakage, ductal obstructions, leakage around T-tube site) in 15 to 20%, portal vein thrombosis in < 5%, hepatic artery thrombosis in 3 to 5% (especially in small children or patients taking sirolimus), hepatic artery mycotic or pseudoaneurysm, and hepatic artery rupture. Typical symptoms include fever, hypotension, and elevated liver function enzymes.

The most common late complications are intrahepatic or anastomotic bile duct strictures, which produce symptoms of cholestasis and cholangitis. Strictures can sometimes be treated endoscopically or through percutaneous transhepatic cholangiographic dilation, stenting, or both, but they often ultimately require retransplantation.

Prognosis

At 1 yr, survival rates with living-donor grafts are 90% for patients and 82% for grafts; rates with deceased-donor grafts are 86% and 82%, respectively. Overall rates for patients and grafts, respectively, are 79% and 72% at 3 yr and 73% and 65% at 5 yr. Survival is better for chronic than for acute liver failure. Death after 1 yr is rare and attributable to a recurrent disorder (eg, cancer, hepatitis) rather than to post-transplantation complications.

Recurrent hepatitis C infection leads to cirrhosis in 15 to 30% of patients by 5 yr. Hepatic disorders with an autoimmune component (eg, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis) recur in 20 to 30% by 5 yr.

Lung Transplantation

Lung transplantation is an option for patients who have respiratory insufficiency or failure and who remain at risk of death despite optimal medical treatment. The most common indications are COPD, idiopathic pulmonary fibrosis, cystic fibrosis, α_1-antitrypsin deficiency, and primary pulmonary hypertension. Less common indications include interstitial lung disorders (eg, sarcoidosis), bronchiectasis, and congenital heart disease. Single and double lung procedures are equally appropriate for most lung disorders without cardiac involvement; the exception is chronic diffuse infection (eg, bronchiectasis), for which double lung transplantation is best. Heart-lung transplantation is indicated for Eisenmenger's syndrome and for any lung disorder with severe ventricular dysfunction likely to be irreversible; cor pulmonale is not an indication because it often reverses after lung transplantation. Single and double lung procedures are about equally common and are at least 8 times more common than heart-lung transplantation.

Relative contraindications include age (single lung recipients must be < 65; double lung recipients, < 60; and heart and lung recipients, < 55), active cigarette smoking, previous thoracic surgery, and, for some cystic fibrosis patients and at some medical centers, lung infection with resistant strains of *Burkholderia cepacia*, which greatly increases mortality risk.

Nearly all donated lungs are from brain-dead, heart-beating donors. Rarely, living adult (usually parent-to-child) lobar transplantation is done when deceased-donor organs are unavailable. Donors must be < 65 and never-smokers and have no active lung disorder as evidenced by

- Oxygenation: PaO_2/FIO_2 (fractional inspired O_2) > 250 to 300, with PaO_2 in mm Hg and FIO_2 in decimal fraction (eg, 0.5)
- Lung compliance: Peak inspiratory pressure < 30 cm H_2O at tidal volume (V_T) 15 mL/kg and positive end-expiratory pressure = 5 cm H_2O
- Gross appearance: Using bronchoscopy

Donor and recipients must be size-matched anatomically (by chest x-ray), physiologically (by total lung capacity), or both.

Timing of referral for transplantation should be determined by factors such as

- Degree of obstructive defect: Forced expiratory volume in 1 sec (FEV_1) < 25 to 30% predicted in patients with COPD, α_1-antitrypsin deficiency, or cystic fibrosis
- PaO_2 < 55 mm Hg
- $PaCO_2$ > 50 mm Hg
- Right atrial pressure > 10 mm Hg and peak systolic pressure > 50 mm Hg for patients with primary pulmonary hypertension
- Progression rate of clinical, radiographic, or physiologic disease

Procedure

The donor is anticoagulated, and a cold crystalloid preservation solution containing prostaglandins is flushed through the pulmonary arteries into the lungs. Donor organs are cooled with iced saline slush in situ or via cardiopulmonary bypass, then removed. Prophylactic antibiotics are often given.

Single lung transplantation requires posterolateral thoracotomy. The native lung is removed, and the bronchus, pulmonary artery, and pulmonary veins of the donor lung are anastomosed to their respective cuffs. The bronchial anastomosis requires intussusception or wrapping with omentum or pericardium to facilitate adequate healing. Advantages include a simpler operation, avoidance of cardiopulmonary

bypass and systemic anticoagulation (usually), more flexibility concerning size matching, and availability of the contralateral lung from the same donor for another recipient. Disadvantages include the possibility of ventilation/perfusion mismatch between the native and transplant lungs and the possibility of poor healing of the single bronchial anastomosis.

Double lung transplantation requires sternotomy or anterior transverse thoracotomy; the procedure is similar to 2 sequential single transplants. The primary advantage is definitive removal of all diseased tissue. The disadvantage is poor healing of the tracheal anastomosis.

Heart-lung transplantation requires median sternotomy with cardiopulmonary bypass. Aortic, right atrial, and tracheal anastomoses are required; the trachea is anastomosed immediately above the bifurcation. The primary advantages are improved graft function and more dependable healing of the tracheal anastomosis because of coronary-bronchial collaterals within the heart-lung block. Disadvantages include long operative time with the need for cardiopulmonary bypass, the need for close size matching, and use of 3 donor organs by one recipient.

Methylprednisolone IV is often given to recipients before reperfusion of the transplanted lung. A common immunosuppressive regimen combines a calcineurin inhibitor (cyclosporine or tacrolimus), a purine metabolism inhibitor (azathioprine or mycophenolate mofetil), and methylprednisolone. Prophylactic antithymocyte globulin (ATG) or OKT3 may also be given during the first 2 wk after transplantation. Corticosteroids may be omitted to facilitate healing of the bronchial anastomosis; higher doses of other drugs (eg, cyclosporine, azathioprine) are substituted. Immunosuppressants are continued indefinitely.

Rejection develops in most patients despite immunosuppressive therapy. Symptoms and signs are similar in hyperacute, acute, and chronic forms and include fever, dyspnea, cough, decreased SaO_2, interstitial infiltrate on x-ray, and a decrease in FEV_1 by > 10 to 15%. Hyperacute rejection must be distinguished from early graft dysfunction caused by ischemic injury during the transplantation procedure. Diagnosis is confirmed if bronchoscopic transbronchial biopsy shows perivascular lymphocytic infiltration in small vessels. IV corticosteroids are usually effective. Treatment of recurrent or resistant cases varies and includes higher corticosteroid doses, aerosolized cyclosporine, ATG, and OKT3.

Chronic rejection (after > 1 yr) occurs in up to 50% of patients; it takes the form of obliterative bronchiolitis or, less commonly, atherosclerosis. Acute rejection may increase risk of chronic rejection. Patients with obliterative bronchiolitis present with cough, dyspnea, and decreased FEV_1 with or without physical and radiographic evidence of an airway process. Differential diagnosis includes pneumonia. Diagnosis is by bronchoscopy with biopsy. No treatment has proved effective, but options include corticosteroids, ATG or OKT3, inhaled cyclosporine, and retransplantation.

The most common surgical complication is poor healing of the bronchial or tracheal anastomosis. Up to 20% of single lung recipients develop bronchial stenosis that causes wheezing and airway obstruction; it can be treated with dilation or stent placement. Other surgical complications include hoarseness and diaphragmatic paralysis, caused by damage to the recurrent laryngeal or phrenic nerves; GI dysmotility, caused by damage to the thoracic vagus nerve; and pneumothorax. Supraventricular arrhythmias develop in some patients, probably because of conduction changes caused by pulmonary vein-atrial suturing.

Prognosis

At 1 yr, survival rates are 84% with living-donor grafts and 83% with deceased-donor grafts. At 5 yr, survival rates are 34% with living-donor grafts and 46% with deceased-donor grafts. Mortality rate is higher for patients with primary pulmonary hypertension, idiopathic pulmonary fibrosis, or sarcoidosis and lower for those with COPD or α_1-antitrypsin deficiency. Mortality rate is higher for single lung transplantation than for double. Most common causes of death within 1 mo are primary graft failure, ischemia and reperfusion injury, and infection (eg, pneumonia) excluding cytomegalovirus; the most common cause between 1 mo and 1 yr is infection; and after 1 yr, it is obliterative bronchiolitis. Mortality risk factors include cytomegalovirus mismatching (donor positive, recipient negative), human leukocyte antigen (HLA-DR) mismatching, diabetes, and prior need for mechanical ventilation or inotropic support. Uncommonly, the disorder recurs, particularly in some patients with an interstitial lung disorder. Exercise

capacity is slightly limited because of a hyperventilatory response.

With heart-lung transplantation, overall survival rate at 1 yr is 60% for patients and grafts.

Pancreas Transplantation

Pancreas transplantation is a form of pancreatic β-cell replacement that can restore normoglycemia in diabetic patients. Because the recipient exchanges risks of insulin injection for risks of immunosuppression, eligibility is limited mostly to patients who have type 1 diabetes with renal failure and who are thus candidates for kidney transplantation; > 90% of pancreas transplantations include transplantation of a kidney. At many centers, failure of standard treatment and episodes of hypoglycemic unawareness are also eligibility criteria. Relative contraindications include age > 55 and significant atherosclerotic cardiovascular disease, defined as history of MI, coronary artery bypass graft surgery, percutaneous coronary intervention, or a positive stress test; these factors dramatically increase perioperative risk.

Options include simultaneous pancreas-kidney (SPK) transplantation; pancreas-after-kidney (PAK) transplantation; and pancreas-alone transplantation. The advantages of SPK are one-time exposure to induction immunosuppression, potential protection of the newly transplanted kidney from adverse effects of hyperglycemia, and the ability to monitor rejection in the kidney; the kidney is more prone to rejection than the pancreas, where rejection is difficult to detect. The advantage of PAK is the ability to optimize HLA matching and timing of kidney transplantation using a living donor. Pancreas-alone transplantation offers an advantage to patients who do not have end-stage renal disease but have other severe diabetes complications, including labile glucose control.

Donors are usually recently deceased patients who are aged 10 to 55 and have no history of glucose intolerance or alcohol abuse. For SPK, the pancreas and kidney come from the same donor, and the same restrictions for kidney donation apply (see p. 1133). A few (< 1%) segmental transplantations from living donors have been done, but this procedure has substantial risks for the donor (eg, splenic infarction, abscess, pancreatitis, pancreatic leak and pseudocyst, secondary diabetes), which limit its widespread use.

Procedure

The donor is anticoagulated, and a cold preservation solution is flushed into the celiac artery. The pancreas is cooled in situ with iced saline slush, then removed en bloc with the liver (for transplantation into a different recipient) and the 2nd portion of the duodenum containing the ampulla of Vater.

The donor pancreas is positioned intraperitoneally and laterally in the lower abdomen. In SPK, the pancreas is placed into the right lower quadrant of the recipient's abdomen and the kidney into the left lower quadrant. The native pancreas is left in place. Anastomoses are made between the donor splenic or superior mesenteric artery and recipient iliac artery and between the donor portal vein and recipient iliac vein. Thus, endocrine secretions drain systemically, causing hyperinsulinemia; sometimes the pancreatic venous system is anastomosed to a portal vein tributary to re-create physiologic conditions, although this procedure is more demanding and its benefits are unclear. The duodenum is sewn to the bladder dome or to the jejunum for drainage of exocrine secretions.

Immunosuppression regimens vary but typically include immunosuppressive Igs, a calcineurin inhibitor, a purine synthesis inhibitor, and corticosteroids, which can be slowly tapered over 12 mo. Despite adequate immunosuppression, rejection develops in 60 to 80% of patients, primarily affecting exocrine, not endocrine, components. Compared with kidney transplantation alone, SPK has a greater risk of rejection, and rejection episodes tend to occur later, to recur more often, and to be corticosteroid-resistant. Symptoms and signs are nonspecific (see Table 128-1).

After SPK and PAK, pancreas rejection, indicated by an increase in serum creatinine, almost always accompanies kidney rejection. After pancreas-alone transplantation, a stable urinary amylase concentration in patients with urinary drainage excludes rejection; a decrease suggests some form of graft dysfunction but is not specific to rejection. Early detection is therefore difficult. Diagnosis is

confirmed by ultrasound-guided percutaneous or cystoscopic transduodenal biopsy. Treatment is with antithymocyte globulin.

Early complications affect 10 to 15% of patients and include wound infection and dehiscence, gross hematuria, intra-abdominal urinary leak, reflux pancreatitis, recurrent UTI, small-bowel obstruction, abdominal abscess, and graft thrombosis. Late complications relate to urinary loss of pancreatic $NaHCO_3^-$, causing volume depletion and non-anion gap metabolic acidosis. Hyperinsulinemia does not appear to adversely affect glucose or lipid metabolism.

Prognosis

At 1 yr, 78% of grafts survive, but > 90% of patients survive. Whether survival is higher than that of patients without transplantation is unclear; however, the primary benefits of the procedure are freedom from insulin therapy and stabilization or amelioration of many diabetic complications (eg, nephropathy, neuropathy). Graft survival is 95% for SPK, 74% for PAK, and 76% for pancreas-alone transplantation. The rate of immunologic graft loss for PAK and pancreas-alone transplants is higher, possibly because such a transplanted pancreas lacks a reliable monitor of rejection; in contrast, rejection after SPK can be monitored using established indicators of rejection for the transplanted kidney.

Pancreatic Islet Cell Transplantation

Islet cell transplantation has theoretical advantages over pancreas transplantation; the most important is that the procedure is less invasive. A secondary advantage is that islet cell transplantation appears to help maintain normoglycemia in patients who require total pancreatectomy for pain due to chronic pancreatitis. Nevertheless, the procedure remains experimental, although steady improvement appears to be occurring.

Its disadvantages are that transplanted glucagon-secreting α cells are nonfunctional (possibly complicating hypoglycemia) and several pancreata are usually required for a single islet cell recipient (exacerbating disparities between graft supply and demand and limiting use of the procedure).

Indications are the same as those for pancreas transplantation. Simultaneous islet cell-kidney transplantation may be desirable after the technique is improved.

Procedure

A pancreas is removed from a brain-dead donor; collagenase is infused into the pancreatic duct to separate islets from pancreatic tissue. A purified islet cell fraction is infused percutaneously into the portal vein. Islet cells travel into hepatic sinusoids, where they lodge and secrete insulin.

Results are best when 2 cadavers are used, with each supplying 2 or 3 infusions of islet cells, followed by an immunosuppressive regimen consisting of an anti-IL-2 receptor, monoclonal antibodies (daclizumab), tacrolimus, and sirolimus. Corticosteroids are not used. Immunosuppression must be continued lifelong or until islet cell function ceases.

Rejection is poorly defined but can be detected by deterioration in blood glucose control; treatment of rejection is not established. Procedural complications include percutaneous hepatic puncture with bleeding, portal vein thrombosis, and portal hypertension.

Successful islet cell transplantation maintains short-term normoglycemia, but long-term outcomes are unknown; additional injections of islet preparations may be necessary to obtain longer-lasting insulin independence.

Small-Bowel Transplantation

Small-bowel transplantation is indicated for patients who have malabsorption because of intestinal disorders (eg, gastroschisis, Hirschsprung's disease, autoimmune enteritis) or intestinal resection (eg, for

mesenteric thromboembolism or extensive Crohn's disease) and who are at high risk of death (usually due to congenital enteropathies such as microvillus inclusion disease) or who develop complications of TPN (eg, liver failure, recurrent sepsis, total loss of venous access). Patients with locally invasive tumors that cause obstruction, abscesses, fistulas, ischemia, or hemorrhage (usually desmoid tumors associated with familial polyposis) are also candidates.

Procedure

Procurement from a brain-dead, beating-heart donor is complex, partly because the small bowel can be transplanted alone, with a liver, or with a stomach, liver, duodenum, and pancreas. The role of living-related donation for small-bowel allografts has yet to be defined. Procedures vary by medical center; immunosuppressive regimens also vary, but a typical regimen includes antilymphocyte globulin for induction, followed by high-dose tacrolimus and mycophenolate mofetil for maintenance.

Weekly endoscopy is indicated to check for rejection. Symptoms and signs of rejection include diarrhea, fever, and abdominal cramping. Endoscopic findings include mucosal erythema, friability, ulceration, and exfoliation; changes are distributed unevenly, may be difficult to detect, and can be differentiated from cytomegalovirus enteritis by viral inclusion bodies. Biopsy findings include blunted villi and inflammatory infiltrates in the lamina propria. Treatment of acute rejection is high-dose corticosteroids, antithymocyte globulin, or both.

Prognosis

Surgical complications affect 50% of patients and include anastomotic leaks, biliary leaks and strictures, hepatic artery thrombosis, and chylous ascites. Nonsurgical complications include graft ischemia and graft-vs-host disease caused by transplantation of gut-associated lymphoid tissue.

At 3 yr, > 50% of grafts with small-bowel transplantation alone survive, but patient survival is around 65%. With liver and small-bowel transplantation, survival rate is lower because the procedure is more extensive and the recipient's condition is more serious.

Tissue Transplantation

Skin allografts: Skin allografts are used for patients with extensive burns or other conditions causing massive skin loss. Allografts are used to cover broad denuded areas and thus reduce fluid and protein losses and discourage invasive infection. The allografts are ultimately rejected, but the resulting denuded areas develop well-vascularized granulations onto which autografts from the patient's healed sites take readily. Skin cells may be grown in culture, then returned to a burned patient to help cover extensive burns; artificial skin, composed of cultured cells on a synthetic underlayer, may also be used. Split-thickness skin grafts are used to accelerate healing of small wounds. A small piece of skin just a few millimeters thick is harvested, and the donor skin is then laid onto the graft site.

Cartilage transplantation: Cartilage transplantation is used for children with congenital nasal or ear defects and adults with severe injuries or joint destruction (eg, severe osteoarthritis). Chondrocytes are more resistant to rejection, possibly because the sparse population of cells in hyaline cartilage is protected from cellular attack by the cartilaginous matrix around them.

Bone transplantation: Bone transplantation is used for reconstruction of large bony defects (eg, after massive resection of bone cancer). No viable donor bone cells survive in the recipient, but dead matrix from allografts can stimulate recipient osteoblasts to recolonize the matrix and lay down new bone. This matrix acts as scaffolding for bridging and stabilizing defects until new bone is formed. Cadaveric allografts are preserved by freezing to decrease immunogenicity of the bone (which is dead at the time of implantation) and by glycerolization to maintain chondrocyte viability. No postimplantation immunosuppressive therapy is used. Although patients develop anti-HLA antibodies, early follow-up detects no evidence of cartilage degradation.

Corneal transplantation: Corneal transplantation is discussed on p. 595.

Adrenal autografting: Adrenal autografting by stereotactically placing medullary tissue within the CNS has been reported to alleviate symptoms in patients with Parkinson's disease. Allografts of adrenal tissue, especially from fetal donors, have also been proposed. Fetal ventral mesencephalic tissue stereotactically implanted in the putamen of patients with Parkinson's disease has been reported to reduce rigidity and bradykinesia. However, with the ethical and political debates about the propriety of using human fetal tissue, a controlled trial large enough to adequately assess fetal neural transplantation appears unlikely. Xenografts of endocrinologically active cells from porcine donors are being tested.

Fetal thymus implants: Fetal thymus implants obtained from stillborn infants may restore immunologic responsiveness in children with thymic aplasia and resulting abnormal development of the lymphoid system. Because the recipient is immunologically unresponsive, immunosuppression is not required; however, severe graft-vs-host disease may occur.