:
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Immune disorders

Introduction

The environment contains thousands of pathogenic microorganisms — viruses, bacteria, fungi, and parasites. Ordinarily, we protect ourselves from infectious organisms and other harmful invaders through an elaborate network of safeguards — the host defense system. Understanding how this system functions provides the framework for studying various immune disorders.

Host defense system

The host defense system includes physical and chemical barriers to infection, the inflammatory response, and the immune response. Physical barriers, such as the skin and mucous membranes, prevent invasion by most organisms. Those organisms that penetrate this first line of defense simultaneously trigger the inflammatory and immune responses. Both responses involve cells derived from a hematopoietic stem cell in the bone marrow.

Chemical barriers include lysozymes (found in body secretions, such as tears, mucus, and saliva) and hydrochloric acid (found in the stomach). Lysozymes destroy bacteria by removing cell walls. Hydrochloric acid breaks down food and mucus that contains pathogens.

The inflammatory response involves polymorphonuclear leukocytes, basophils, mast cells, platelets and, to some extent, monocytes and macrophages.

The immune response primarily involves the interaction of lymphocytes (T and B), macrophages, and macrophagelike cells and their products. These cells may be circulating or may be localized in the immune system's tissues and organs, including the thymus, lymph nodes, spleen, and tonsils. The thymus participates in the maturation of T lymphocytes (cell-mediated immunity); here these cells are “educated” to differentiate “self” from “nonself.” In contrast, B lymphocytes (humoral immunity) mature in the bone marrow. The key humoral effector mechanism is the production of immunoglobulin by B cells and the subsequent activation of the complement cascade. The lymph nodes, spleen, liver, and intestinal lymphoid tissue help remove and destroy circulating antigens in the blood and lymph.

Antigens

An antigen is any substance that can induce an immune response. T and B lymphocytes have specific receptors that respond to specific antigen molecular shapes (epitopes). In B cells, this receptor is an immunoglobulin (Ig) (antibody) cell: IgD or IgM, sometimes referred to as a surface immunoglobulin. The T-cell antigen receptor recognizes antigens only in association with specific cell surface molecules known as the major histocompatibility complex (MHC). (See *The major histocompatibility complex*, page 430.) MHC molecules, which differ among individuals, identify substances as self or nonself. Slightly different antigen receptors can recognize a phenomenal number of distinct antigens, which are coded by distinct, variable region genes.

Groups, or clones, of lymphocytes exist with identical receptors for a specific antigen. The clone of a lymphocyte rapidly proliferates when exposed to the specific antigen. Some lymphocytes further differentiate, and others become memory cells, which allow a more rapid response — the memory or anamnestic response — to subsequent challenge by the antigen.

Many factors influence antigenicity. Among them are the antigen's physical and chemical characteristics, its relative foreignness, and the individual's genetic makeup, particularly the MHC molecules. Most antigens are large molecules, such as proteins or polysaccharides. (Smaller molecules such as drugs that aren't antigenic by themselves are known as haptens. These haptens can bind with larger molecules, or

carriers, and become antigenic or immunogenic.) The antigen's relative foreignness influences the immune response's intensity. For example, little or no immune response may follow transfusion of serum proteins between humans; however, a vigorous immune response (serum sickness) commonly follows transfusion of horse serum proteins to a human. Genetic makeup may also determine why some individuals respond to certain antigens, whereas others

don't. The genes responsible for this phenomenon encode the MHC molecules.

THE MAJOR HISTOCOMPATIBILITY COMPLEX

The major histocompatibility complex (MHC) is a cluster of genes on human chromosome 6 that plays a pivotal role in the immune response. Also known as *human leukocyte antigen (HLA) genes,* these genes are inherited in an autosomal codominant manner. That is, each individual receives one set of MHC genes (haplotype) from each parent, and both sets of genes are expressed on the individual's cells. These genes play a role in the recognition of self versus nonself and the interaction of immunologically active cells by coding for cell-surface proteins.

HLA antigens are divided into three classes. Class I antigens appear on nearly all of the body's cells and include HLA-A, HLA-B, and HLA-C antigens. During tissue graft rejection, they're the chief antigens recognized by the host. When killer ($CD8^+$) T cells use a virally infected antigen, they recognize it in the context of a class I antigen. Class II antigens only appear on B cells, macrophages, and activated T cells. They include the HLA-D and HLA-DR antigens. Class II antigens promote efficient collaboration between immunocompetent cells.

Helper ($CD4^+$) T cells require that antigen be presented in the context of a class II antigen. Because these

antigens also determine whether an individual responds to a particular antigen, they're also known as immune response genes. Class III antigens include certain complement proteins (C2, C4, and Factor B).

B lymphocytes

B lymphocytes and their products, immunoglobulins, contribute to humoral immunity. The binding of soluble antigen with B-cell antigen receptors initiates the humoral immune response. The activated B cells differentiate into plasma cells that secrete immunoglobulins or antibodies. This response is regulated by T lymphocytes and their products, lymphokines. These lymphokines, which include interleukin (IL)-2, IL-4, IL-5, and interferon (IFN) 8, are important in determining the class of immunoglobulins made by B cells.

The immunoglobulins secreted by plasma cells are four-chain molecules with two heavy (H) and two light (L) chains. (See *Structure of the immunoglobulin molecule*.) Each chain has a variable (V) region and one or more constant (C) regions, which are coded by separate genes. The V regions of both L and H chains participate in the binding of antigens. The C regions of the H chain provide a binding site for crystallizable fragment (Fc) receptors on cells and govern other mechanisms.

Any clone of B cells has one antigen specificity determined by the V regions of its L and H chains. However, the clone can change the class of immunoglobulin that it makes by changing the association between its V region genes and H chain C region genes (a process known as isotype switching). For example, a clone of B cells genetically preprogrammed to recognize tetanus toxoid initially will make an IgM antibody against tetanus toxoid and later an IgG or other antibody against it.

The five known classes of immunoglobulins — IgG, IgM, IgA, IgE, and IgD — are distinguished by the constant portions of their H chains. However, each class has a kappa or a lambda L chain, which gives rise to many subtypes. The almost limitless combinations of L and H chains give immunoglobulins their specificity.

- *IgG,* the smallest immunoglobulin, appears in all body fluids because of its ability to move across membranes as a single structural unit (a

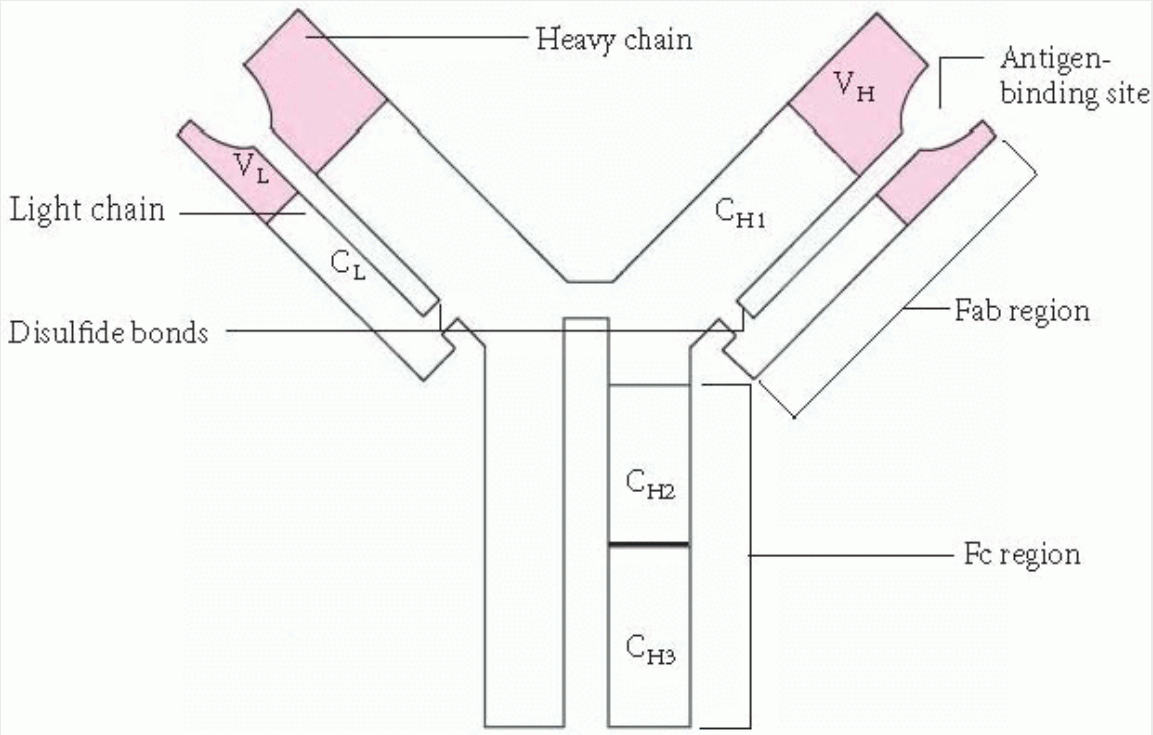
monomer). It constitutes 75% of total serum immunoglobulins and is the major antibacterial and antiviral antibody.

- *IgM,* the largest immunoglobulin, appears as a pentamer (five monomers joined by a J-chain). Unlike IgG — which is produced mainly in the secondary, or recall, response — IgM dominates in the primary, or initial, immune response. However, like IgG, IgM is involved in classic antibody reactions, including precipitation, agglutination, neutralization, and complement fixation. Because of its size, IgM can't readily cross membrane barriers and is usually present only in the vascular system. IgM constitutes 5% of total serum immunoglobulins.
- *IgA* exists in serum primarily as a monomer; in secretory form, IgA exists almost exclusively as a dimer (two monomer molecules joined by a J-chain and a secretory component chain). As a secretory immunoglobulin, IgA defends external body surfaces and is present in colostrum, saliva, tears, nasal fluids, and respiratory, GI, and genitourinary secretions. This antibody is considered important in preventing antigenic agents from attaching to epithelial surfaces. IgA makes up 20% of total serum immunoglobulins.
- *IgE,* present in trace amounts in serum, is involved in the release of vasoactive amines stored in basophils and tissue mast cell granules. When released, these bioamines cause the allergic effects characteristic of this type of hypersensitivity (erythema, itching, smooth-muscle contraction, secretions, and swelling).
- *IgD,* present as a monomer in serum in minute amounts, is the predominant antibody found on the surface of B lymphocytes and serves mainly as an antigen receptor. It may function in controlling lymphocyte activation or suppression.

STRUCTURE OF THE IMMUNOGLOBULIN MOLECULE

The immunoglobulin molecule consists of four polypeptide chains — two heavy (H) and two light (L) chains — held together by disulfide bonds. The H chain has one variable (V) and at least three constant (C) regions. The L chain has one V and one C region.

Together, the V regions of the H and L chains form a pocket known as the antigen-binding site. This site is located within the antigen-binding fragment (Fab) region of the molecule. Part of the C region of the H chains forms the crystallizable fragment (Fc) region of the molecule. This region mediates effector mechanisms such as complement activation and is the portion of the immunoglobulin molecule bound by Fc receptors on phagocytic cells, mast cells, and basophils. Each immunoglobulin molecule also has two antibody-combining sites (except for the immunoglobulin [Ig] M molecule, which has 10, and IgA, which may have two or more).



T lymphocytes

T lymphocytes and macrophages are the chief participants in cell-mediated immunity. Immature T lymphocytes are derived from the bone marrow. Upon migration to the thymus, they undergo a maturation

process that is dependent upon products of the MHC, human leukocyte antigen (HLA) genes. Thus, mature T cells can distinguish between self and nonself. T cells acquire certain surface molecules, or markers; these markers combined with the T-cell antigen receptor promote the particular activation of each type of T cell. T-cell activation requires presentation of antigens in the context of a specific HLA antigen. Helper T cells require class II HLA antigens; cytotoxic T cells require class I HLA antigens. T-cell activation also involves IL-1, produced by macrophages, and IL-2, produced by T cells.

Natural killer (NK) cells are a discrete population of large lymphocytes, some of which resemble T cells. NK cells recognize surface changes on body cells infected with a virus; they then bind to and, in many cases, kill the infected cells.

Macrophages

Important cells of the reticuloendothelial system, macrophages influence both immune and inflammatory responses. Macrophage precursors circulate in the blood. When they collect in various tissues and organs, they differentiate into macrophages with varying characteristics. Unlike B and T lymphocytes, macrophages lack surface receptors for specific antigens; instead, they have receptors for the C region of the H chain (Fc region) of immunoglobulin, for fragments of the third component of complement (C3), and for nonimmunologic factors such as carbohydrate molecules.

One of the most important functions of macrophages is the presentation of antigen to T lymphocytes. Macrophages ingest and process antigen, then deposit it on their own surfaces in association with HLA antigen. T lymphocytes become activated upon recognizing this complex. Macrophages also function in the inflammatory response by producing IL-1, which generates fever. Additionally, macrophages synthesize complement proteins and other mediators that produce phagocytic, microbicidal, and tumoricidal effects.

Cytokines

Cytokines are low-molecular-weight proteins involved in communication between cells. Their purpose is to induce or regulate a variety of

immune or inflammatory responses. However, disorders may occur if cytokine production or regulation is impaired. Cytokines are categorized as follows:

- *Colony-stimulating factors* function primarily as hematopoietic growth factors, guiding the division and differentiation of bone marrow stem cells. They also influence the functioning of mature lymphocytes, monocytes, macrophages, and neutrophils.
- *Interferons* act early to limit the spread of viral infections. They also inhibit tumor growth. Mainly, they determine how well tissue cells interact with cytotoxic cells and lymphocytes.
- *Interleukins* are a large group of cytokines. (Those produced primarily by T lymphocytes are called lymphokines. Those produced by mononuclear phagocytes are called monokines.) They have a variety of effects, but most direct other cells to divide and differentiate.
- *Tumor necrosis factors* are believed to play a major role in mediating inflammation and cytotoxic reactions (along with IL-1, IL-6, and IL-8).
- *Transforming growth factor* demonstrates both inflammatory and anti-inflammatory effects. It's believed to be partially responsible for tissue fibrosis associated with many

  diseases. It demonstrates immunosuppressive effects on T cells, B cells, and NK cells.

Complement system

The chief humoral effector of the inflammatory response, the complement system consists of more than 20 serum proteins. When activated, these proteins interact in a cascadelike process that has profound biological effects. Complement activation takes place through one of two pathways. In the classical pathway, binding of IgM or IgG and antigen forms antigen-antibody complexes that activate the first complement component, C1. This, in turn, activates C4, C2, and C3. In the alternate pathway, activating surfaces such as bacterial membranes directly amplify spontaneous cleavage of C3. Once C3 is activated in either pathway, activation of the terminal components — C5 to C9 — follows.

The major biological effects of complement activation include phagocyte attraction (chemotaxis) and activation, histamine release, viral neutralization, promotion of phagocytosis by opsonization, and lysis of cells and bacteria. Other mediators of inflammation derived from the kinin and coagulation pathways interact with the complement system.

Polymorphonuclear leukocytes

Besides macrophages and complement, other key participants in the inflammatory response are the polymorphonuclear leukocytes (also known as *granulocytes*) — neutrophils, eosinophils, and basophils.

Neutrophils, the most numerous of these cells, derive from bone marrow and increase dramatically in number in response to infection and inflammation. Highly mobile cells, neutrophils are attracted to areas of inflammation (chemotaxis); in fact, they're the primary constituent of pus.

Neutrophils have surface receptors for immunoglobulin and complement fragments, and they avidly ingest opsonized particles such as bacteria. Ingested organisms are then promptly killed by toxic oxygen metabolites and enzymes such as lysozyme. Unfortunately, neutrophils not only kill invading organisms but may also damage host tissues.

Also derived from bone marrow, *eosinophils* multiply in both allergic disorders and parasitic infestations. Although their phagocytic function isn't clearly understood, evidence suggests that they participate in host defense against parasites. Their products may also diminish the inflammatory response in allergic disorders.

Two other types of cells that function in allergic disorders are basophils and mast cells. (Mast cells, however, aren't blood cells.) *Basophils* circulate in peripheral blood, whereas *mast cells* accumulate in connective tissue, particularly in the lungs, intestines, and skin. Both types of cells have surface receptors for IgE. When crosslinked by an IgE-antigen complex, they release mediators characteristic of the allergic response.

Immune disorders

Because of their complexity, the processes involved in host defense and immune response may malfunction. When the body's defenses are exaggerated, misdirected, or either absent or depressed, the result may be a hypersensitivity disorder, autoimmunity, or immunodeficiency, respectively. Some forms of immunodeficiency are iatrogenic (See *Iatrogenic immunodeficiency,* pages 434 and 435.)

Hypersensitivity disorders

An exaggerated or inappropriate immune response may lead to various hypersensitivity disorders. Such disorders are classified as type I through type IV, although some overlap exists. (See *Classification of hypersensitivity reactions,* pages 436 and 437.)

TYPE I HYPERSENSITIVITY (ALLERGIC DISORDERS)

In individuals with type I hypersensitivity, certain antigens (allergens) activate T cells. These, in turn, induce B-cell production of IgE, which binds to the Fc receptors on the surface of mast cells. When these cells are re-exposed to the same antigen, the antigen binds with the surface IgE, cross-links the Fc receptors, and causes mast cell degranulation with release of various mediators. (Degranulation may also be triggered by complement-derived anaphylatoxins— C3a and C5a — or by certain drugs such as morphine.)

IATROGENIC IMMUNODEFICIENCY

Iatrogenic immunodeficiency may be a complicating adverse effect of chemotherapy or other treatments. At times, though, it's the goal of therapy—for example, to suppress immune-mediated tissue damage in autoimmune disorders or to prevent rejection of an organ transplant.

As explained below, iatrogenic immunodeficiency may be induced by immunosuppressive drugs, radiation therapy, or splenectomy.

Immunosuppressive drug therapy

Immunosuppressive drugs fall into several categories:

- Cytotoxic drugs. These drugs kill immunocompetent cells while they're replicating. However, most cytotoxic drugs aren't selective and thus interfere with all rapidly proliferating cells. As a result, they reduce the number of lymphocytes as well as phagocytes. Besides depleting their number, cytotoxic drugs interfere with lymphocyte synthesis and release of immunoglobulins and lymphokines.

  Cyclophosphamide, a potent and commonly used immunosuppressant, initially depletes the number of B cells, suppressing humoral immunity. However, chronic therapy also depletes T cells, suppressing cell-mediated immunity as well. Cyclophosphamide may be used in systemic lupus erythematosus, Wegener's granulomatosis, other systemic vasculitides, and in certain autoimmune disorders. Because it nonselectively destroys rapidly dividing cells, this drug can cause severe bone marrow suppression with neutropenia, anemia, and thrombocytopenia; gonadal suppression with sterility; alopecia; hemorrhagic cystitis; and nausea, vomiting, and stomatitis. It may also increase the risk of lymphoproliferative neoplasms.

  Among other cytotoxic drugs used for immunosuppression are azathioprine (commonly used in kidney transplantation) and methotrexate (occasionally used in rheumatoid arthritis and other autoimmune disorders).

  If the patient is receiving cytotoxic drugs, monitor his white blood cell (WBC) count. If it falls too low, the drug dosage may need to be adjusted. Also monitor urine output and watch for signs of cystitis, especially if

the patient is taking cyclophosphamide. Ensure adequate fluid intake (2 qt [about 2 L] daily). Give mesna as ordered to help prevent hemorrhagic cystitis. Provide antiemetics to relieve nausea and vomiting as ordered. Give meticulous oral hygiene and report signs of stomatitis.

Teach the patient about the early signs and symptoms of infection. If his WBC count falls too low, granulocyte colony-stimulating factor may be used to boost the count. Make sure the male patient understands the risk of sterility; advise sperm banking if appropriate. Young women may take hormonal contraceptives to minimize ovarian dysfunction and to prevent pregnancy during administration of these potentially teratogenic drugs.

- Corticosteroids. These adrenocortical hormones are used to treat immune-mediated disorders because of their potent anti-inflammatory and immunosuppressive effects. Corticosteroids stabilize the vascular membrane, blocking tissue infiltration by neutrophils and monocytes, thus inhibiting inflammation. They also "kidnap" T cells in the bone marrow, causing lymphopenia. Because these drugs aren't cytotoxic, lymphocyte concentration can return to normal within 24 hours after they're withdrawn. Corticosteroids also appear to inhibit immunoglobulin synthesis and to interfere with the binding of immunoglobulin to antigen or to cells with crystallizable fragment receptors. These drugs have many other effects as well.

  The most commonly used oral corticosteroid is prednisone. For long-term therapy, prednisone is best given early in the morning to minimize exogenous suppression

of cortisol production and with food or milk to minimize gastric irritation. After the acute phase, it's usually reduced to an alternate-day schedule and then gradually withdrawn to minimize potentially harmful adverse effects. Other corticosteroids used for immunosuppression include hydrocortisone, methylprednisolone, and dexamethasone.

Chronic corticosteroid therapy can cause numerous adverse effects, which are sometimes more harmful than the disease itself. Neurologic adverse effects include euphoria, insomnia, or psychosis; cardiovascular effects include hypertension and edema; and GI effects include gastric irritation, ulcers, and increased appetite with weight gain. Other possible effects are cataracts, hyperglycemia, glucose intolerance, muscle weakness, osteoporosis, delayed wound healing, and increased susceptibility to infection.

During corticosteroid therapy, monitor the patient's blood pressure, weight, intake and output, and blood glucose. Instruct the patient to eat a well-balanced, low-salt diet or to follow the specially prescribed diet to prevent excessive weight gain. Remember that even though the patient is more susceptible to infection, he'll show fewer or less dramatic signs of inflammation.

- Cyclosporine. Cyclosporine selectively suppresses the proliferation and development of helper T cells, resulting in depressed cell-mediated immunity. This drug is used primarily to prevent rejection of kidney, liver, and heart transplants but is also being investigated for use in several other disorders. Significant toxic effects of cyclosporine primarily involve

the liver and kidney, so treatment with this drug requires regular evaluation of renal and hepatic function. Adjusting the dose or the duration of therapy helps minimize certain adverse effects.

- Antilymphocyte serum or antithymocyte globulin (ATG). This anti-T cell antibody reduces T-cell number and function, thus suppressing cell-mediated immunity. It has been used effectively to prevent cell-mediated rejection of tissue grafts or transplants. Usually, ATG is administered immediately before the transplant and continued for some time afterward. Potential adverse effects include anaphylaxis and serum sickness. Occurring 1 to 2 weeks after injection of ATG, serum sickness is characterized by fever, malaise, rash, arthralgias and, occasionally, glomerulonephritis or vasculitis. It presumably results from the deposition of immune complexes throughout the body.

Radiation therapy

Because irradiation is cytotoxic to proliferating and intermitotic cells, including most lymphocytes, radiation therapy may induce profound lymphopenia, resulting in immunosuppression. Irradiation of all major lymph node areas — a procedure known as total nodal irradiation — is used to treat certain disorders such as Hodgkin's lymphoma. Its effectiveness in severe rheumatoid arthritis, lupus nephritis, and the prevention of kidney transplant rejection is still under investigation.

Splenectomy

Splenectomy may be performed to manage various disorders, including splenic injury or trauma, tumor, Hodgkin's lymphoma, hairy cell leukemia, Felty's syndrome Gaucher's disease, idiopathic thrombocytopenic purpura, hereditary spherocytosis and

hereditary elliptocytosis, thalassemia major, and chronic lymphocytic leukemia.

After splenectomy, the patient has increased susceptibility to infection. These patients should receive the pneumococcal vaccine polyvalent (Pneumovax) for prophylaxis and be warned to avoid exposure to infection and trauma.

CLASSIFICATION OF HYPERSENSITIVITY REACTIONS

Type	Cause	Antibody or cell involved	Pathophysiology	Clinical examples
I - Immediate hypersensitivity (anaphylaxis, atopy)	Foreign protein (antigen)	Immunoglobulin (Ig) E	IgE attaches to the surface of the mast cell and specific antigen, triggers release of intracellular granules from mast cells	Extrinsic asthma, allergic rhinitis, anaphylaxis, reactions to stinging insects, some food and drug reactions
II - Cytotoxic hypersensitivity	Foreign protein (antigen)	IgG or IgM	IgG or IgM reacts with antigen, activates complement, and causes cytolysis or phagocytosis	Transfusion reaction, hemolytic drug reaction, Goodpasture's syndrome, hemolytic disease of the neonate
III - Immune complex disease	Foreign protein (antigen) Endogenous antigens	IgG, IgM, IgA	Antigen-antibody complexes precipitate in tissue, activate complement, and cause	Rheumatoid arthritis, systemic lupus erythematosus, serum sickness to some drugs or

			inflammatory reaction	viral hepatitis antigen, glomerulonephritis
IV - Delayed cell-mediated	Foreign protein, cell, or tissue	T lymphocytes	Sensitized T-cells react with specific antigen to induce inflammatory process by direct cell action or by activity of lymphokines	Contact dermatitis, graft-versus-host disease, granulomatous diseases

Some of these mediators are preformed, whereas others are newly synthesized upon activation of mast cells. Preformed mediators include heparin, histamine, proteolytic and other enzymes, and chemotactic factors for eosinophils and neutrophils. Newly synthesized mediators include prostaglandins and leukotrienes. Mast cells also produce a variety of cytokines. The effects of these mediators include smooth-muscle contraction, vasodilation, bronchospasm, edema, increased vascular permeability, mucus secretion, and cellular infiltration by eosinophils and neutrophils. Among classic associated signs and symptoms are hypotension, wheezing, swelling, urticaria, and rhinorrhea.

Examples of type I hypersensitivity disorders are anaphylaxis, atopy (an allergic reaction related to genetic predisposition), hay fever (allergic rhinitis) and, in some cases, asthma.

TYPE II HYPERSENSITIVITY (ANTIBODY-DEPENDENT CYTOTOXICITY)

In type II hypersensitivity, antibody is directed against cell surface antigens. (Alternately, though, antibody may be directed against small molecules adsorbed to cells or against cell surface receptors rather than against cell constituents themselves.) Type II hypersensitivity then causes tissue damage through several mechanisms. Binding of antigen and antibody activates complement, which ultimately disrupts cellular membranes.

Another mechanism is mediated by various phagocytic cells with receptors for immunoglobulin (Fc region) and complement fragments. These cells envelop and destroy (phagocytose) opsonized targets, such as red blood cells, leukocytes, and platelets. Antibody against these cells may be visualized by immunofluorescence. Cytotoxic T cells and NK cells also contribute to tissue damage in type II hypersensitivity.

Examples of type II hypersensitivity include transfusion reactions, hemolytic disease of the neonate, autoimmune hemolytic anemia, Goodpasture's syndrome, and myasthenia gravis.

TYPE III HYPERSENSITIVITY (IMMUNE COMPLEX DISEASE)

In type III hypersensitivity, excessive circulating antigen-antibody complexes (immune

complexes) result in the deposition of these complexes in tissue — most commonly in the kidneys, joints, skin, and blood vessels. (Normally, immune complexes are effectively cleared by the reticuloendothelial system.) These deposited immune complexes activate the complement cascade, resulting in local inflammation. They also trigger platelet release of vasoactive amines that increase vascular permeability, augmenting deposition of immune complexes in vessel walls.

Type III hypersensitivity may be associated with infections, such as hepatitis B and bacterial endocarditis; certain cancers in which a serum sickness-like syndrome may occur; and autoimmune disorders such as lupus erythematosus. This hypersensitivity reaction may also follow drug or serum therapy.

TYPE IV HYPERSENSITIVITY (DELAYED HYPERSENSITIVITY)

In type IV hypersensitivity, antigen is processed by macrophages and presented to T cells. The sensitized T cells then release lymphokines, which recruit and activate other lymphocytes, monocytes, macrophages, and polymorphonuclear leukocytes. The coagulation, kinin, and

complement pathways also contribute to tissue damage in this type of reaction.

Examples of type IV hypersensitivity include tuberculin reactions, contact hypersensitivity, and sarcoidosis.

Autoimmune disorders

Autoimmunity is characterized by a misdirected immune response in which the body's defenses become self-destructive. Autoimmune diseases aren't transmitted from one person to another, and the causes of autoimmunity aren't clearly understood. However, the process of autoimmunity is related to genes or a combination of genes, hormones, and environmental stimuli. Individuals with specific genes or gene combinations may be at a higher risk for developing autoimmune disorders, which may be triggered by outside stimuli, such as sun exposure, infection, drugs, or pregnancy.

Recognition of self through the MHC is of primary importance in an immune response. However, how an immune response against self is prevented and which cells are primarily responsible isn't well understood.

Many autoimmune disorders are characterized by B-cell hyperactivity, marked by proliferation of B cells and autoantibodies and by hypergammaglobulinemia. B-cell hyperactivity is probably related to T-cell abnormalities, but the molecular basis of autoimmunity is poorly understood. Hormonal and genetic factors strongly influence the incidence of autoimmune disorders; for example, lupus erythematosus predominantly affects females of childbearing age, and certain HLA haplotypes are associated with an increased risk of specific autoimmune disorders.

Autoimmune diseases may not follow a clear pattern of symptoms; therefore, a definitive diagnosis may be delayed. Diagnosis may rely on the patient's medical history; family history; physical examination, including signs and symptoms; and laboratory tests. Autoantibodies are usually found with such disorders as rheumatoid arthritis or systemic lupus erythematosus, but confusion may occur because individuals with these disorders may have false negative results to laboratory tests.

Treatment for autoimmune disorders focuses on relieving symptoms, preserving organ function, and providing medication that can target the immune system, such as cyclophosphamide and cyclosporine. Autoimmune and immunological disorders are being researched. Web sites for the National Institutes of Health *(www.nih.gov)* and other organizations offer substantial health care information relevant to both the patient and the physician.

Immunodeficiency

In immunodeficiency, the immune response is absent or depressed, resulting in increased susceptibility to infection. This disorder may be primary or secondary. Primary immunodeficiency reflects a defect involving T cells, B cells, or lymphoid tissues. The National Primary Immunodeficiency Resource Center is a source of information on primary immunodeficiency syndromes.

Secondary immunodeficiency results from an underlying disease or factor that depresses or blocks the immune response. The most common forms of immunodeficiency are caused by viral infection (as in acquired immunodeficiency syndrome).

ALLERGY

Asthma

Asthma is a reversible lung disease characterized by obstruction or narrowing of the airways, which are typically inflamed and hyperresponsive to a variety of stimuli. It may resolve spontaneously or with treatment. Its symptoms range from mild wheezing and dyspnea to life-threatening respiratory failure. (See *Determining asthma's severity*.) Symptoms of bronchial airway obstruction may persist between acute episodes.

Causes and incidence

Asthma that results from sensitivity to specific external allergens is known as *extrinsic*. In cases in which the allergen isn't obvious, asthma is referred to as *intrinsic*. Allergens that cause extrinsic asthma include

pollen, animal dander, house dust or mold, kapok or feather pillows, food additives containing sulfites, and any other sensitizing substance. Extrinsic (atopic) asthma usually begins in childhood and is accompanied by other manifestations of atopy (type I, immunoglobulin [Ig] E-mediated allergy), such as eczema and allergic rhinitis. In intrinsic (nonatopic) asthma, no extrinsic allergen can be identified. Most cases are preceded by a severe respiratory infection. Irritants, emotional stress, fatigue, exposure to noxious fumes as well as changes in endocrine, temperature, and humidity may aggravate intrinsic asthma attacks. In many asthmatics, intrinsic and extrinsic asthma coexist.

Several drugs and chemicals may provoke an asthma attack without using the IgE pathway. Apparently, they trigger release of mast-cell mediators by way of prostaglandin inhibition. Examples of these substances include aspirin, various nonsteroidal anti-inflammatory drugs (such as indomethacin and mefenamic acid), and tartrazine, a yellow food dye. Exercise may also provoke an asthma attack. In exercise-induced asthma, bronchospasm may follow heat and moisture loss in the upper airways.

The allergic response has two phases. When the patient inhales an allergenic substance, sensitized IgE antibodies trigger mast-cell degranulation in the lung interstitium, releasing histamine, cytokines, prostaglandins, thromboxanes, leukotrienes, and eosinophil chemotaxic factors. Histamine then attaches to receptor sites in the larger bronchi, causing irritation, inflammation, and edema. In the late phase, inflammatory cells flow in. The influx of eosinophils provides additional inflammatory mediators and contributes to local injury.

Although this common condition can strike at any age, half of all cases first occur in children younger than age 10; in this age-group, asthma affects twice as many males as females. In the United States, 14 million adults and 6 million children have asthma. Emergency department visits, hospitalizations, and mortality from asthma have been increasing for more than 20 years, especially among children and blacks.

DETERMINING ASTHMA'S SEVERITY

Asthma is classified by severity using these features:

- frequency, severity, and duration of symptoms

- degree of airflow obstruction (spirometry measure) or peak expiratory flow (PEF)
- frequency of nighttime symptoms and the degree that the asthma interferes with daily activities.

Severity can change over time, and even milder cases can become severe in an uncontrolled attack. Long-term therapy depends on whether the patient's asthma is classified as mild intermittent, mild persistent, moderate persistent, or severe persistent. For all patients, quick relief can be obtained by using a short-acting bronchodilator (2 to 4 puffs of short-acting inhaled $beta_2$-adrenergic agonists as needed for symptoms). However, the use of a short-acting bronchodilator more than twice a week in patients with intermittent asthma or daily or increasing use in patients with persistent asthma may indicate the need to initiate or increase long-term control therapy.

Mild intermittent asthma

The signs and symptoms of mild intermittent asthma include:

- daytime symptoms no more than twice a week
- nighttime symptoms no more than twice a month
- lung function testing (either PEF or forced expiratory volume in 1 second) is 80% of predicted value or higher
- PEF varies no more than 20%.

Severe exacerbations, separated by long, symptomless periods of normal lung function, indicate mild intermittent asthma. A course of systemic corticosteroids is recommended for these exacerbations; otherwise, daily medication isn't required.

Mild persistent asthma

The signs and symptoms of mild persistent asthma include:

- daytime symptoms 3 to 6 days a week
- nighttime symptoms 3 to 4 times a month
- lung function testing is 80% of predicted value or higher
- PEF varies between 20% and 30%.

The preferred treatment for mild, persistent asthma is low-dose inhaled corticosteroids, but alternative treatments include cromolyn, leukotriene modifier, nedocromil, or sustained-release theophylline.

Moderate persistent asthma

The signs and symptoms of moderate persistent asthma include:

- daily daytime symptoms
- at least weekly nighttime symptoms
- lung function testing is 60% to 80% of predicted value
- PEF varies more than 30%.

The preferred treatment for moderate persistent asthma is low- or medium-dose inhaled corticosteroids combined with a long-acting inhaled $beta_2$-adrenergic agonist.

Alternative treatments include increasing inhaled corticosteroids within the medium-dose range or lowor medium-dose inhaled corticosteroids with either leukotriene modifier or theophylline.

For recurring exacerbations, the preferred treatment is to increase inhaled corticosteroids within the medium-dose range and add a long-acting inhaled $beta_2$-adrenergic agonist. The alternative treatment is to increase inhaled corticosteroids within the medium-dose range and add either leukotriene modifier or theophylline.

Severe persistent asthma

The signs and symptoms of severe persistent asthma include:

- continual daytime symptoms
- frequent nighttime symptoms
- lung function testing is 60% of predicted value or lower
- PEF varies more than 30%.

The preferred treatment for severe, persistent asthma includes high-dose inhaled corticosteroids combined with long-acting inhaled $beta_2$-adrenergic agonists. Long-term administration of corticosteroid tablets or syrup (2 mg/kg/day, not to exceed 60 mg/day), may be used to reduce the need for systemic corticosteroid therapy.

Complications

- Status asthmaticus
- Respiratory failure

Signs and symptoms

An asthma attack may begin dramatically, with simultaneous onset of many severe symptoms, or insidiously, with gradually increasing respiratory distress. It typically includes progressively worsening shortness of breath, cough, wheezing, and chest tightness or some combination of these signs or symptoms.

During an acute attack, the cough sounds tight and dry. As the attack subsides, tenacious mucoid sputum is produced (except in young children, who don't expectorate). Characteristic wheezing may be accompanied by coarse rhonchi, but fine crackles aren't heard unless associated with a related complication. Between acute attacks, breath sounds may be normal.

The intensity of breath sounds in symptomatic asthma is typically reduced. A prolonged phase of forced expiration is typical of airflow obstruction. Evidence of lung hyperinflation (use of accessory muscles, for example) is particularly common in children. Acute attacks may be accompanied by tachycardia, tachypnea, and diaphoresis. In severe attacks, the patient may be unable to speak more than a few words without pausing for breath. Cyanosis, confusion, and lethargy indicate the onset of respiratory failure.

Diagnosis

Laboratory studies in patients with asthma commonly show these abnormalities:

- Pulmonary function studies reveal signs of airway obstruction (decreased peak expiratory flow rates and forced expiratory volume in 1 second), low-normal or decreased vital capacity, and increased total lung and residual capacity. However, pulmonary function studies may be normal between attacks.
- Pulse oximetry may reveal decreased arterial oxygen saturation (SaO_2).
- Arterial blood gas (ABG) analysis provides the best indications of an attack's severity. In acutely severe asthma, the partial pressure of arterial oxygen is less than 60 mm Hg, the partial pressure of arterial carbon dioxide ($PaCO_2$) is 40 mm Hg or more, and pH is usually decreased.
- Complete blood count with differential reveals increased eosinophil count.
- Chest X-rays may show hyperinflation with areas of focal atelectasis.

Before initiating tests for asthma, rule out other causes of airway obstruction and wheezing. In children, such causes include cystic fibrosis, tumors of the bronchi or mediastinum, and acute viral bronchitis; in adults, other causes include obstructive pulmonary disease, heart failure, and epiglottitis.

Treatment

Treatment of acute asthma aims to decrease bronchoconstriction, reduce bronchial airway edema, and increase pulmonary ventilation. After an acute episode, treatment focuses on avoiding or removing precipitating factors, such as environmental allergens or irritants.

If asthma is known to be caused by a particular antigen, it may be treated by desensitizing the patient through a series of injections of limited amounts of the antigen. The aim is to curb the patient's immune response to the antigen.

If asthma results from an infection, antibiotics are prescribed. Drug therapy is most effective when begun soon after the onset of signs and symptoms. For relief of symptoms in adults and children older than age 5, short-acting inhaled $beta_2$-adrenergic agonists for bronchodilation may be used, and a course of systemic corticosteroids may be needed. The goal of therapy is asthma control with minimal or no adverse effects from medication.

Acute attacks that don't respond to self-treatment may require hospital care, $beta_2$-adrenergic agonists by inhalation or subcutaneous injection (in three doses over 60 to 90 minutes) and, possibly, oxygen for hypoxemia. If the patient responds poorly, systemic corticosteroids and, possibly, subcutaneous epinephrine may help. $Beta_2$-adrenergic agonist inhalation continues hourly. I.V. aminophylline may be added to the regimen and I.V. fluid therapy is started. Patients who don't respond to this treatment, whose airways remain obstructed, and who have increasing respiratory difficulty are at risk for status asthmaticus and may require mechanical ventilation.

Treatment of status asthmaticus consists of aggressive drug therapy with a $beta_2$-adrenergic agonist by nebulizer every 30 to 60 minutes, possibly supplemented with subcutaneous epinephrine, I.V. corticosteroids, I.V. aminophylline, oxygen administration, I.V. fluid therapy, and intubation and mechanical ventilation for hypercapnic respiratory failure ($PaCO_2$ of 40 mm Hg or more). (See *How status asthmaticus progresses*, pages 442 and 443.)

Special considerations

During an acute attack, proceed as follows:

- First, assess the severity of asthma.
- Administer the prescribed treatments and assess the patient's response.
- Place the patient in high Fowler's position. Encourage pursed-lip and diaphragmatic breathing. Help him to relax.
- Administer prescribed humidified oxygen by nasal cannula at 2 L/minute to ease breathing and to increase SaO_2. Later, adjust oxygen according to the patient's vital signs and ABG levels.
- Anticipate intubation and mechanical ventilation if the patient fails to maintain adequate oxygenation.
- Monitor serum theophylline levels to ensure they're in the therapeutic range. Observe your patient for signs and symptoms of theophylline toxicity (vomiting, diarrhea, and headache), as well as for signs of subtherapeutic dosage (respiratory distress and increased wheezing).
- Observe the frequency and severity of your patient's cough, and note whether it's productive. Then auscultate his lungs, noting adventitious or absent breath sounds. If his cough isn't productive and rhonchi are present, teach him effective coughing techniques. If the patient can tolerate postural drainage and chest percussion, perform these procedures to clear secretions. Suction an intubated patient as needed.
- Treat dehydration with I.V. fluids until the patient can tolerate oral fluids, which will help loosen secretions.
- If conservative treatment fails to improve the airway obstruction, anticipate bronchoscopy or bronchial lavage when a lobe or larger area collapses.

ALERT

Monitor the patient's vital signs. Keep in mind that developing or increasing tachypnea may indicate worsening asthma or drug toxicity. Blood pressure readings may reveal pulsus paradoxus, indicating severe

asthma. Hypertension may indicate asthma-related hypoxemia.

During long-term care, proceed as follows:

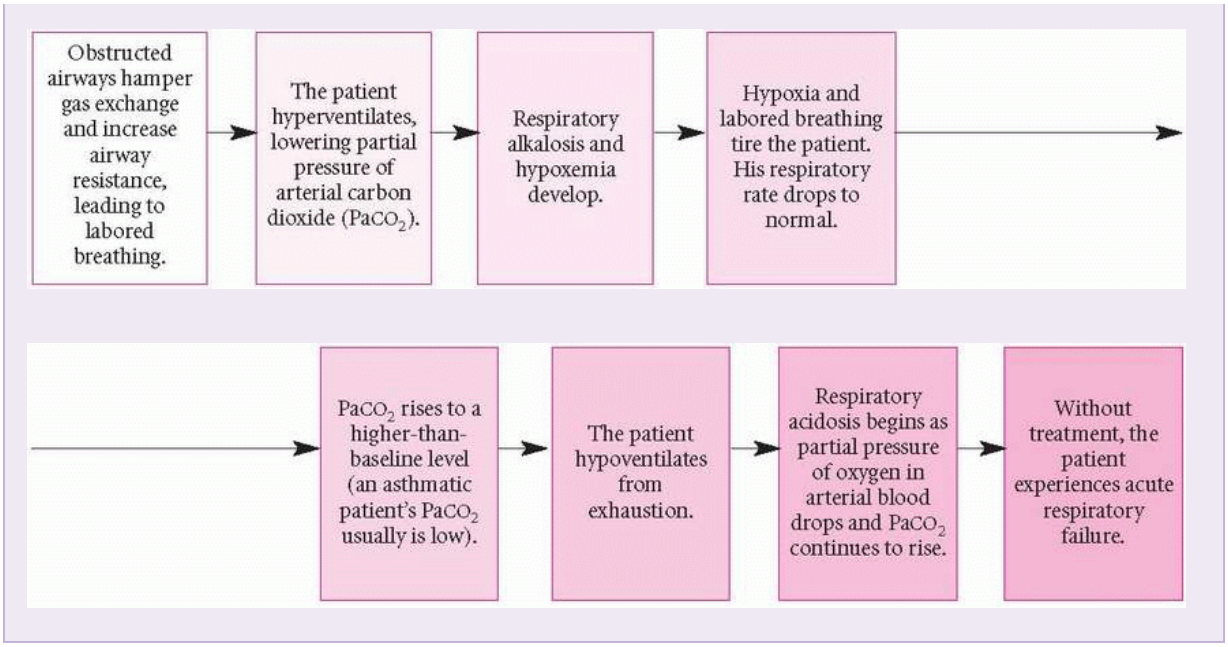
- Monitor the patient's respiratory status to detect baseline changes, to assess response to treatment, and to prevent or detect complications.
- Auscultate the lungs frequently, noting the degree of wheezing and quality of air movement.
- Review ABG levels, pulmonary function test results, and SaO_2 readings.
- If the patient is taking systemic corticosteroids, observe for complications, such as

  elevated blood glucose levels and friable skin and bruising.
- Cushingoid effects resulting from long-term use of corticosteroids may be minimized by alternate-day dosage or use of prescribed inhaled corticosteroids.
- If the patient is taking corticosteroids by inhaler, watch for signs of candidal infection in the mouth and pharynx. Using an extender device and rinsing the mouth afterward may prevent this.
- Observe the patient's anxiety level. Keep in mind that measures that reduce hypoxemia and breathlessness should help relieve anxiety.
- Keep the room temperature comfortable and use an air conditioner or a fan in hot, humid weather.
- Control exercise-induced asthma by instructing the patient to use a bronchodilator or cromolyn 30 minutes before exercise. Also instruct him to use pursed-lip breathing while exercising.

PATHOPHYSIOLOGY

HOW STATUS ASTHMATICUS PROGRESSES

A potentially fatal complication, status asthmaticus arises when impaired gas exchange and heightened airway resistance increase the work of breathing. This flow chart shows the stages of status asthmaticus.



All patients should know the following:

- Teach the patient and his family to avoid known allergens and irritants.
- Describe to the patient prescribed drugs, including their names, dosages, actions, adverse effects, and special instructions.
- Teach the patient how to use a metereddose inhaler. If he has difficulty using an inhaler, he may need an extender device to optimize drug delivery and lower the risk of candidal infection with orally inhaled corticosteroids.
- If the patient has moderate to severe asthma, explain how to use a peak flow meter to measure the degree of airway obstruction. Tell him to keep a record of peak flow readings and to bring it to medical appointments. Explain the importance of calling the physician at once if the peak flow drops suddenly (may signal severe respiratory problems).
- Tell the patient to notify the physician if he develops a fever above 100° F (37.8° C), chest pain, shortness of breath without coughing or exercising, or uncontrollable coughing. An uncontrollable asthma attack requires immediate attention.
- Teach the patient diaphragmatic and pursed-lip breathing as well as effective coughing techniques.

- Urge him to drink at least 3 qt (3 L) of fluids daily to help loosen secretions and maintain hydration.

Allergic rhinitis

Allergic rhinitis is a reaction to airborne (inhaled) allergens. Depending on the allergen, the resulting rhinitis and conjunctivitis may occur seasonally (hay fever) or year-round (perennial allergic rhinitis).

Causes and incidence

Hay fever reflects an immunoglobulin (Ig) E-mediated type I hypersensitivity response to an environmental antigen (allergen) in a genetically susceptible individual. In most cases, it's induced by windborne pollens: in the spring by tree pollens (oak, elm, maple, alder, birch, and cottonwood), in the summer by grass pollens (sheep sorrel and English plantain), and in the fall by weed pollens (ragweed). Occasionally, hay fever is induced by allergy to fungal spores. In addition to individual sensitivity and geographical differences in plant population, the amount of pollen in the air can be a factor in determining whether symptoms develop. Hot, dry, windy days have more pollen than cool, damp, rainy days.

In perennial allergic rhinitis, inhaled allergens provoke antigen responses that produce recurring symptoms year-round. The allergens trigger antibody production and histamine release, producing itching, swelling, and mucus. The major perennial allergens and irritants include dust mites, feather pillows, mold, cigarette smoke, upholstery, and animal dander. Seasonal pollen allergy may exacerbate signs and symptoms of perennial rhinitis.

Allergic rhinitis is the most common atopic allergic reaction, affecting more than 20 million Americans. It's most prevalent in young children and adolescents but can occur in all age groups.

Complications

- Secondary sinus and middle ear infections
- Nasal polyps

- Nasal obstruction

Signs and symptoms

In seasonal allergic rhinitis, the key signs and symptoms are paroxysmal sneezing, profuse watery rhinorrhea, nasal obstruction or congestion, and pruritus of the nose and eyes. It's usually accompanied by pale, cyanotic, edematous nasal mucosa; red and edematous eyelids and conjunctivae; excessive lacrimation; and headache or sinus pain. Some patients also complain of itching in the throat and malaise.

In perennial allergic rhinitis, conjunctivitis and other extranasal effects are rare, but chronic nasal obstruction is common. In many cases, this obstruction extends to eustachian tube obstruction, particularly in children.

In both types of allergic rhinitis, dark circles may appear under the patient's eyes (“allergic shiners”) because of venous congestion in the maxillary sinuses. The severity of signs and symptoms may vary from season to season and from year to year.

Diagnosis

Microscopic examination of sputum and nasal secretions reveals large numbers of eosinophils. Blood chemistry shows normal or elevated IgE. A definitive diagnosis is based on the patient's personal and family history of allergies as well as physical findings during a symptomatic phase. Skin testing paired with tested responses to environmental stimuli can pinpoint the responsible allergens given the patient's history. In patients who can't tolerate skin testing, the radioallergosorbent test may be helpful in determining specific allergen sensitivity.

To distinguish between allergic rhinitis and other nasal mucosa disorders, remember these differences:

- In chronic vasomotor rhinitis, eye symptoms are absent, rhinorrhea is mucoid, and seasonal variation is absent.
- In infectious rhinitis (the common cold), the nasal mucosa is beet red; nasal secretions contain polymorphonuclear, not eosinophilic,

exudate; and signs and symptoms include fever and sore throat. This condition isn't a recurrent seasonal phenomenon.

- In rhinitis medicamentosa, which results from excessive use of nasal sprays or drops, nasal drainage and mucosal redness and swelling disappear when such medication is withheld.

PEDIATRIC TIP

In children, differential diagnosis involves ruling out a nasal foreign body, such as a bean or a button.

Treatment

Treatment aims to control symptoms by eliminating the environmental antigen, if possible, and providing drug therapy and immunotherapy.

Antihistamines block histamine effects but commonly produce anticholinergic adverse effects (sedation, dry mouth, nausea, dizziness, blurred vision, and nervousness). Antihistamines, such as cetirizine, loratadine, and fexofenadine, produce fewer adverse effects and are less likely to cause sedation.

Inhaled intranasal steroids produce local anti-inflammatory effects with minimal systemic adverse effects. The most commonly used intranasal steroids are fluticasone, mometasone, and triamcinolone. These drugs are effective when symptoms aren't relieved by antihistamines alone.

Advise the patient to use intranasal steroids regularly as prescribed for optimal effectiveness. Cromolyn may be helpful in treating hay fever, but this drug may take up to 4 weeks to produce a satisfactory effect and must be taken regularly during allergy season. Eye drop versions of cromolyn and antihistamines are available for itchy, bloodshot eyes.

Long-term management includes immunotherapy, or desensitization with injections of extracted allergens, administered before or during allergy season or perennially. Seasonal allergies require particularly close dosage regulation.

Special considerations

- Before desensitization injections, assess the patient's symptom status. Afterward, watch for adverse reactions, including anaphylaxis and severe localized erythema.

ALERT

Keep epinephrine and emergency resuscitation equipment available, and observe the patient for 30 minutes after the injection. Instruct the patient to call the physician if a delayed reaction should occur.

The following protocol is recommended for allergic rhinitis:

- Monitor the patient's compliance with prescribed drug treatment regimens. Also carefully note any changes in the control of his symptoms or any signs of drug misuse.
- To reduce environmental exposure to airborne allergens, suggest that the patient sleep with the windows closed, avoid the countryside during pollination seasons, use air conditioning to filter allergens and minimize moisture and dust, and eliminate dust-collecting items, such as wool blankets, deep-pile carpets, and heavy drapes, from the home.
- In severe and resistant cases, suggest that the patient consider drastic changes in lifestyle such as relocation to a pollen-free area either seasonally or year-round.

- Be aware that some patients may develop chronic complications, including sinusitis and nasal polyps.

Atopic dermatitis

Atopic dermatitis is a chronic skin disorder that's characterized by superficial skin inflammation and intense itching. Although this disorder may appear at any age, it typically begins during infancy or early childhood. It may then subside spontaneously, followed by exacerbations in late childhood, adolescence, or early adulthood. Atopic dermatitis affects 2.5% of the population.

Causes and incidence

The cause of atopic dermatitis is still unknown. However, several theories attempt to explain its pathogenesis. One theory suggests an underlying metabolically or biochemically induced skin disorder that's genetically linked to elevated serum immunoglobulin (Ig) E levels. Another theory suggests defective T-cell function.

Exacerbating factors of atopic dermatitis include irritants, infections (commonly caused by *Staphylococcus aureus*), and some allergens. Although no reliable link exists between atopic dermatitis and exposure to inhalant allergens (such as house dust and animal dander), exposure to food allergens (such as soybeans, fish, or nuts) may coincide with flare-ups of atopic dermatitis.

Complications

- Scarring
- Secondary infection

Signs and symptoms

Scratching the skin causes vasoconstriction and intensifies pruritus, resulting in erythematous, weeping lesions. Eventually, the lesions become scaly and lichenified. Usually, they're located in areas of flexion and extension, such as the neck, antecubital fossa, popliteal folds, and behind the ears. Patients with atopic dermatitis are prone to unusually severe viral infections, bacterial and fungal skin infections, ocular complications, and allergic contact dermatitis.

Diagnosis

Typically, the patient has a history of atopy, such as asthma, hay fever, or urticaria; his family may have a similar history. Laboratory tests reveal eosinophilia and elevated serum IgE levels. A skin biopsy may be performed, but it isn't always required to make the diagnosis.

Treatment

Measures to ease this chronic disorder include meticulous skin care, environmental control of offending allergens, and drug therapy. Because dry skin aggravates itching, frequent application of nonirritating topical lubricants is important, especially after bathing or showering. Minimizing exposure to allergens and irritants, such as wools and harsh detergents, also helps control symptoms.

Drug therapy involves corticosteroids and antipruritics. Active dermatitis responds well to topical corticosteroids, which should be applied immediately after bathing for optimal penetration. Oral antihistamines are commonly used to help control itching. A bedtime dose may reduce involuntary scratching during sleep. If secondary infection develops, antibiotics are necessary. A newer treatment is the use of topical immunomodulators; these agents are steroid-free and have demonstrated an 80% success rate in studies.

Special considerations

- Monitor the patient's compliance with drug therapy.
- Teach the patient when and how to apply topical corticosteroids.
- Emphasize the importance of regular personal hygiene using only water with little soap.
- Be alert for signs and symptoms of secondary infection; teach the patient how to recognize them as well.
- If the patient's diet is modified to exclude food allergens, monitor his nutritional status.
- Offer support to help the patient and his family cope with this chronic disorder.
- Discourage use of laundry additives.
- Dissuade the patient from scratching during urticaria to help prevent an infection.

PRODUCTS THAT CONTAIN LATEX

Many medical and everyday items contain latex, which can be a threat to the patient with latex allergy. The

most common items that contain latex are listed below.

Medical products

- Adhesive bandages
- Airways, nasogastric tubes
- Blood pressure cuff, tubing, and bladder
- Catheters
- Catheter leg straps
- Dental dams
- Elastic bandages
- Electrode pads
- Fluid-circulating hypothermia blankets
- Handheld resuscitation bag
- Hemodialysis equipment
- I.V. catheters
- Latex or rubber gloves
- Medication vials
- Pads for crutches
- Protective sheets
- Reservoir breathing bags
- Rubber airway and endotracheal tubes
- Stethoscopes
- Tape
- Tourniquets

Nonmedical products

- Adhesive tape
- Balloons (excluding Mylar)
- Cervical diaphragms
- Condoms
- Dishwashing gloves

- Disposable diapers
- Elastic stockings
- Glue
- Latex paint
- Nipples and pacifiers
- Racquet handles
- Rubber bands
- Tires

Latex allergy

Latex is a substance found in an increasing number of products both on the job and in the home environment. Also increasing is the number of latex allergies. Latex allergy is a hypersensitivity reaction to products that contain natural latex, which is derived from the sap of a rubber tree, not synthetic latex. These hypersensitivity reactions range from local dermatitis to a life-threatening anaphylactic reaction.

Causes and incidence

About 1% of the population has a latex allergy. Anyone who is in frequent contact with latex-containing products is at risk for developing a latex allergy. (See *Products that contain latex*.) The more frequent the exposure, the higher the risk. The populations at highest risk are medical and dental professionals, workers in latex companies, and patients with spina bifida.

Other individuals at risk include:

- patients with a history of asthma or other allergies, especially to bananas, avocados, tropical fruits, or chestnuts
- patients with a history of multiple intra-abdominal or genitourinary surgeries
- patients who require frequent intermittent urinary catheterization.

Complications

- Respiratory obstruction
- Systemic vascular collapse

Signs and symptoms

Early signs that a life-threatening hypersensitivity reaction may be occurring include hypotension, tachycardia, and oxygen desaturation. Other clinical findings include urticaria, flushing, bronchospasm, difficulty breathing, pruritus, palpitations, abdominal pain, and syncope. Mild signs and symptoms may include itchy skin, swollen lips, nausea, diarrhea, and red, swollen, teary eyes.

Diagnosis

A patient who describes even the mildest symptoms during a history and physical assessment should be suspected of having a latex allergy. The patient may describe dermatitis or mild respiratory distress when using latex gloves, inflating a balloon, or coming in contact with other latex products.

CONFIRMING DIAGNOSIS

A blood test for latex sensitivity can confirm the diagnosis. This test, which measures specific immunoglobulin E antibodies against latex, should be used only when latex allergy is suspected; it isn't recommended as a screening tool.

Treatment

The best treatment of latex allergy is prevention; the more a latex-sensitive person is exposed to latex, the worse his symptoms will become. To avoid exposure, advise the patient to substitute products made of silicone and vinyl for those made of latex.

When a latex allergy is suspected or known, the patient may receive medications before and after surgery or other invasive procedures. Premedications may include prednisone, diphenhydramine, and cimetidine. Postmedications may include hydrocortisone, diphenhydramine, and famotidine.

There's no known treatment for an allergic reaction to latex. Care is supportive in nature. The patient's airway, breathing, and circulation must be monitored. An artificial airway, oxygen therapy, cardiopulmonary resuscitation, and fluid management may be necessary. During an acute reaction, epinephrine, diphenhydramine, and hydrocortisone are commonly administered by I.V. infusion.

Special considerations

- Urge the patient to wear an identification tag mentioning his latex allergy.
- Teach the patient and family members how to use an epinephrine autoinjector.
- Teach the patient to be aware of all latex-containing products and to use vinyl or silicone products instead. Advise him that Mylar balloons don't contain latex.

PREVENTION

- *Make sure that items that aren't available in a latex-free form, such as stethoscopes and blood pressure cuffs, are wrapped in cloth before they come in contact with a hypersensitive patient's skin.*
- *Place the patient in a private room or with another patient who requires a latex-free environment.*
- *When adding medication to an I.V. bag, inject the drug through the spike port, not the rubber latex port.*

Anaphylaxis

Anaphylaxis is a dramatic, acute atopic reaction marked by the sudden onset of rapidly progressive urticaria and respiratory distress. A severe

reaction may precipitate vascular collapse, leading to systemic shock and, sometimes, death.

Causes and incidence

The source of anaphylactic reactions is ingestion of or other systemic exposure to sensitizing drugs or other substances. Such substances may include serums (usually horse serum), vaccines, allergen extracts, enzymes (L-asparaginase), hormones, penicillin and other antibiotics, sulfonamides, local anesthetics, salicylates, polysaccharides, diagnostic chemicals (sulfobromophthalein, sodium dehydrocholate, and radiographic contrast media), foods (especially legumes, nuts, berries, seafood, and egg albumin) and sulfite-containing food additives, insect venom (honeybees, wasps, hornets, yellow jackets, fire ants, mosquitoes, and certain spiders) and, rarely, ruptured hydatid cyst.

A common cause of anaphylaxis is penicillin, which induces anaphylaxis in 1 to 4 of every 10,000 patients treated with it. Penicillin is most likely to induce anaphylaxis after parenteral administration or prolonged therapy and in atopic patients with an allergy to other drugs or foods. (See *Preventing allergic response to penicillin*, page 448.) An anaphylactic reaction requires previous sensitization or exposure to the specific antigen, resulting in the production of specific immunoglobulin (Ig) E antibodies by plasma cells. This antibody production takes place in the lymph nodes and is enhanced by helper T cells. IgE antibodies then bind to membrane receptors on mast cells (found throughout connective tissue) and basophils.

PREVENTION

PREVENTING ALLERGIC RESPONSE TO PENICILLIN

When administering penicillin or its derivatives, such as ampicillin or carbenicillin, follow these recommendations from the World Health Organization to prevent an allergic response:

- Have an emergency kit available to treat allergic reactions.

- Take a detailed patient history, including penicillin allergy and other allergies. In an infant younger than age 3 months, check for penicillin allergy in the mother.
- Never give penicillin to a patient who has had an allergic reaction to it.
- Before giving penicillin to a patient with suspected penicillin allergy, refer the patient for skin and immunologic tests to confirm it.
- Always tell a patient he's going to receive penicillin before he takes the first dose.
- Observe the patient carefully for adverse effects for at least one half-hour after penicillin administration.
- Be aware that penicillin derivatives also may elicit an allergic reaction.

On re-exposure, the antigen binds to adjacent IgE antibodies or cross-linked IgE receptors, activating a series of cellular reactions that trigger degranulation — the release of powerful chemical mediators (such as histamine, eosinophil chemotactic factor of anaphylaxis, and plateletactivating factor) from mast cell stores. IgG or IgM enters into the reaction and activates the release of complement fractions.

At the same time, two other chemical mediators, bradykinin and leukotrienes, induce vascular collapse by stimulating contraction of certain groups of smooth muscles and by increasing vascular permeability. In turn, increased vascular permeability leads to decreased peripheral resistance and plasma leakage from the circulation to extravascular tissues (which lowers blood volume, causing hypotension, hypovolemic shock, and cardiac dysfunction).

Complications

- Respiratory obstruction
- Systemic vascular collapse
- Death

Signs and symptoms

An anaphylactic reaction produces sudden physical distress within seconds or minutes (although a delayed or persistent reaction may occur for up to 24 hours) after exposure to an allergen. The reaction's severity is inversely related to the interval between exposure to the allergen and the onset of symptoms. Usually, the first symptoms include a feeling of impending doom or fright, weakness, sweating, sneezing, shortness of breath, nasal pruritus, urticaria, and angioedema, followed rapidly by symptoms in one or more target organs.

Cardiovascular symptoms include hypotension, shock and, sometimes, cardiac arrhythmias. If untreated, arrhythmia may precipitate circulatory collapse. Respiratory symptoms can occur at any level in the respiratory tract and commonly include nasal mucosal edema, profuse watery rhinorrhea, itching, nasal congestion, and sudden sneezing attacks. Edema of the upper respiratory tract results in hypopharyngeal and laryngeal obstruction (hoarseness, stridor, and dyspnea). This is an early sign of acute respiratory failure, which can be fatal. GI and genitourinary symptoms include severe stomach cramps, nausea, diarrhea, and urinary urgency and incontinence.

Diagnosis

Anaphylaxis can be diagnosed by the rapid onset of severe respiratory or cardiovascular

signs and symptoms after ingestion or injection of a drug, vaccine, diagnostic agent, food, or food additive or after an insect sting. If these symptoms occur without a known allergic stimulus, rule out other possible causes of shock (acute myocardial infarction, status asthmaticus, or heart failure).

Treatment

Anaphylaxis is always an emergency. It requires an *immediate* injection of epinephrine 1:1,000 aqueous solution, 0.1 to 0.5 ml, repeated every 5 to 20 minutes as needed.

In the early stages of anaphylaxis, when the patient hasn't lost consciousness and is normotensive, give epinephrine I.M. or subcutaneously and help it move into circulation faster by massaging the injection site. In severe reactions, when the patient has lost consciousness and is hypotensive, give epinephrine I.V.

ALERT

Maintain airway patency. Observe the patient for early signs of laryngeal edema (hoarseness, stridor, and dyspnea), which will probably require endotracheal tube insertion or a tracheotomy and oxygen therapy.

In case of cardiac arrest, begin cardiopulmonary resuscitation, including closedchest heart massage, assisted ventilation, and other therapies as indicated by clinical response.

Watch for hypotension and shock, and maintain circulatory volume with volume expanders (plasma, plasma expanders, saline, and albumin) as needed. Stabilize blood pressure with the I.V. vasopressors norepinephrine and dopamine. Monitor blood pressure, central venous pressure, and urine output as a response index.

After the initial emergency, administer other medications as ordered: subcutaneous epinephrine, longer-acting epinephrine, corticosteroids, and I.V. diphenhydramine for long-term management and I.V. aminophylline over 10 to 20 minutes for bronchospasm.

ALERT

Rapid infusion of aminophylline may cause or aggravate severe hypotension.

Special considerations

PREVENTION

- *Teach the patient to avoid exposure to known allergens. A person allergic to certain foods or drugs must learn to avoid the offending food or drug in all its forms. A person allergic to insect stings should avoid open fields and wooded areas during the insect season.*

An anaphylaxis kit (epinephrine, antihistamine, and tourniquet) should also be carried whenever the patient with known severe allergic reactions goes outdoors. In addition, every patient prone to anaphylaxis should wear a medical identification bracelet identifying his allergies.

- *If a patient must receive a drug to which he's allergic, prevent a severe reaction by making sure he receives careful desensitization with gradually increasing doses of the antigen or advance administration of steroids. Of course, a person with a known allergic history should receive a drug with a high anaphylactic potential only after cautious pretesting for sensitivity. Closely monitor the patient during testing, and make sure you have resuscitative equipment and epinephrine ready. When any patient needs a drug with a high anaphylactic potential (particularly parenteral drugs), make sure he receives each dose under close medical observation.*
- *Closely monitor a patient undergoing diagnostic tests that use radiographic contrast media, such as excretory urography, cardiac catheterization, and angiography.*

Urticaria and angioedema

Urticaria, commonly known as hives, is an episodic, usually self-limited skin reaction characterized by local dermal wheals surrounded by an erythematous flare. Angioedema is a subcutaneous and dermal eruption that produces deeper, larger wheals (usually on the hands, feet, lips, genitals, and eyelids) and a more diffuse swelling of loose subcutaneous tissue. Urticaria and angioedema can occur simultaneously, but angioedema may last longer.

HEREDITARY ANGIOEDEMA

A nonallergenic type of angioedema, hereditary angioedema results from an autosomal dominant trait — a hereditary deficiency of an alpha globulin, the normal inhibitor of C1 esterase (a component of the complement system). This deficiency allows uninhibited C1 esterase release, resulting in the vascular changes common to angioedema.

The clinical effects of hereditary angioedema usually appear in childhood with recurrent episodes of subcutaneous or submucosal edema at irregular intervals of weeks, months, or years, in many cases after trauma or stress. Hereditary angioedema is unifocal, without urticarial pruritus, but associated with recurrent edema of the skin and mucosa (especially of the GI and respiratory tracts). GI tract involvement may cause nausea, vomiting, and severe abdominal pain. Laryngeal angioedema may cause fatal airway obstruction.

Treatment of acute hereditary angioedema may require androgens such as danazol. Tracheotomy may be necessary to relieve airway obstruction resulting from laryngeal angioedema.

Causes and incidence

Urticaria and angioedema are common allergic reactions that may occur in 20% of the general population. The causes of these reactions include allergy to drugs, foods, insect bites and stings and, occasionally, inhalant allergens (animal dander and cosmetics) that provoke an immunoglobulin (Ig) E-mediated response to protein allergens. However, certain drugs may cause urticaria without an IgE response. When urticaria and angioedema are part of an anaphylactic reaction, they almost always persist long after the systemic response has subsided. This occurs because circulation to the skin is the last to be restored after an allergic reaction, which results in slow histamine reabsorption at the reaction site.

Nonallergic urticaria and angioedema are also related to histamine release. External physical stimuli, such as cold (usually in young adults), heat, water, or sunlight, may also provoke urticaria and angioedema. *Dermographism urticaria,* which develops after stroking or scratching of the skin, occurs in as much as 20% of the population. Such urticaria develops with varying pressure, usually under tight clothing, and is aggravated by scratching.

Several different mechanisms and underlying disorders may provoke urticaria and angioedema. These include IgE-induced release of mediators from cutaneous mast cells; binding of IgG or IgM to antigen, resulting in complement activation; and such disorders as localized or secondary infections (such as respiratory infection), neoplastic diseases (such as Hodgkin's lymphoma), connective tissue diseases (such as systemic lupus erythematosus), collagen vascular diseases, and psychogenic diseases.

Complications

- Infection from scratching
- Laryngeal edema (upper respiratory tract involvement)
- Severe abdominal colic (GI involvement)

Signs and symptoms

The characteristic features of urticaria are distinct, raised, evanescent (temporary) dermal wheals surrounded by an erythematous flare. These lesions may vary in size. In cholinergic urticaria, the wheals may be tiny and blanched, surrounded by erythematous flares.

Angioedema characteristically produces nonpitted swelling of deep subcutaneous tissue, usually on the eyelids, lips, genitalia, and mucous membranes. These swellings don't usually itch but may burn and tingle.

Diagnosis

An accurate patient history can help determine the cause of urticaria. Such a history should include:

- drug history, including over-the-counter preparations (vitamins, aspirin, and antacids)
- frequently ingested foods (strawberries, milk products, fish)
- environmental influences (pets, carpet, clothing, soap, inhalants, cosmetics, hair dye, and insect bites and stings).

Diagnosis also requires physical assessment to rule out similar conditions as well as a complete blood count, urinalysis, erythrocyte sedimentation rate, and a chest X-ray to rule out inflammatory infections. Skin testing, an elimination diet, and a food diary (recording time and amount of food eaten and circumstances) can pinpoint provoking allergens. The food diary may also suggest other allergies. For instance, a patient allergic to fish may also be allergic to iodine contrast materials.

Recurrent angioedema without urticaria, along with a familial history, points to hereditary angioedema. (See *Hereditary angioedema*.) Decreased serum levels of complement 4 and complement 1 esterase inhibitors confirm this diagnosis.

Treatment

Treatment aims to prevent or limit contact with triggering factors or, if this is impossible, to desensitize the patient to them and to relieve symptoms. During desensitization, progressively larger doses of specific antigens (determined by skin testing) are injected intradermally. After the triggering stimulus has been removed, urticaria usually subsides in a few days — except for drug reactions, which may persist as long as the drug is in the bloodstream.

Diphenhydramine, hydroxyzine, or another antihistamine can ease itching and swelling in every kind of urticaria. Corticosteroid therapy may be necessary for some patients.

Special considerations

- Inform the patient receiving antihistamines of the possibility of drowsiness.
- Suggest cool compresses to reduce swelling and pain. A cool bath may be used for large areas. Calamine lotion may be soothing as well.

- Avoid hot baths, which can cause hives to return.
- Advise the patient to avoid tight-fitting clothing.

Blood transfusion reaction

Mediated by immune or nonimmune factors, a transfusion reaction accompanies or follows I.V. administration of blood components. Its severity varies from mild (fever and chills) to severe (acute renal failure or complete vascular collapse and death), depending on the amount of blood transfused, the type of reaction, and the patient's general health.

Causes and incidence

Hemolytic reactions follow transfusion of mismatched blood. Transfusion of serologically incompatible blood triggers the most serious reaction, marked by intravascular agglutination of red blood cells (RBCs). The recipient's antibodies (immunoglobulin [Ig] G or IgM) attach to the donated RBCs, leading to widespread clumping and destruction of the recipient's RBCs and, possibly, the development of disseminated intravascular coagulation (DIC) and other serious effects.

Transfusion of Rh-incompatible blood triggers a less serious reaction within several days to 2 weeks. Rh reactions are most common in females sensitized to RBC antigens by prior pregnancy or by unknown factors (such as bacterial or viral infection) and in people who have received more than five transfusions. (See *Understanding the Rh system*, page 452.)

Allergic reactions are fairly common but only occasionally serious. In this type of reaction, transfused soluble antigens react with surface IgE molecules on mast cells and basophils, causing degranulation and release of allergic mediators. Antibodies against IgA in an IgA-deficient recipient can also trigger a severe allergic reaction (anaphylaxis).

Febrile nonhemolytic reactions, the most common type of reaction, apparently develop when cytotoxic or agglutinating antibodies in the recipient's plasma attack antigens on transfused lymphocytes, granulocytes, or plasma cells.

UNDERSTANDING THE RH SYSTEM

The Rh system contains more than 30 antibodies and antigens. Eighty-five percent of the world's population is Rh-positive, which means that the red blood cells of most people carry the D or Rh antigen. The remaining 15% of the population, who are Rh-negative, don't carry this antigen.

When Rh-negative people receive Rh-positive blood for the first time, they become sensitized to the D antigen but show no immediate reaction to it. If they receive Rh-positive blood a second time, they then develop a massive hemolytic reaction. For example, an Rh-negative mother who delivers an Rh-positive baby is sensitized by the baby's Rh-positive blood. During her next Rh-positive pregnancy, her sensitized blood would cause a hemolytic reaction in fetal circulation. Thus, the Rh-negative mother should receive Rh_o (D) immune globulin (human) I.M. within 72 hours after delivering an Rh-positive baby to prevent formation of antibodies against Rh-positive blood.

Although fairly uncommon, *bacterial contamination* of donor blood can occur during donor phlebotomy. Offending organisms are usually gram-negative, especially *Pseudomonas* species, *Citrobacter freundii,* and *Escherichia coli*.

Contamination of donor blood with viruses, such as hepatitis, cytomegalovirus, and malaria, is also possible.

Complications

- Bronchospasm
- Respiratory failure
- Acute tubular necrosis
- Acute renal failure
- Anaphylactic shock

- Vascular collapse
- Disseminated intravascular coagulation

Signs and symptoms

Immediate effects of a hemolytic transfusion reaction develop within a few minutes or hours after the start of the transfusion and may include chills, fever, urticaria, tachycardia, dyspnea, nausea, vomiting, tightness in the chest, chest and back pain, hypotension, bronchospasm, angioedema, and signs and symptoms of anaphylaxis, shock, pulmonary edema, heart failure, and renal failure. In a surgical patient under anesthesia, these symptoms are masked, but blood oozes from mucous membranes or the incision site.

Delayed hemolytic reactions can occur up to several weeks after a transfusion, causing fever, an unexpected fall in serum hemoglobin (Hb) level, and jaundice.

Allergic reactions are typically afebrile and characterized by urticaria and angioedema, possibly progressing to cough, respiratory distress, nausea, vomiting, diarrhea, abdominal cramps, vascular instability, shock, and coma.

The hallmark of febrile nonhemolytic reactions is mild to severe fever that may begin at the start of transfusion or within 2 hours after its completion.

Bacterial contamination produces a high fever, nausea, vomiting, diarrhea, abdominal cramps and, possibly, shock. Symptoms of viral contamination may not appear for several weeks after transfusion.

Diagnosis

CONFIRMING DIAGNOSIS

Confirming a hemolytic transfusion reaction requires proof of blood incompatibility and evidence of hemolysis, such as hemoglobinuria, anti-A or anti-B antibodies in the serum, low serum Hb levels, and elevated bilirubin levels.

If you suspect such a reaction, have the patient's blood retyped and crossmatched with the donor's blood. After a hemolytic transfusion reaction, laboratory tests will show increased indirect bilirubin levels, decreased haptoglobin levels, increased serum Hb levels, and Hb in the urine. As the reaction progresses, tests may show

signs of DIC (thrombocytopenia, increased prothrombin time, and decreased fibrinogen level) and acute tubular necrosis (increased blood urea nitrogen and serum creatinine levels).

A blood culture to isolate the causative organism should be done when bacterial contamination is suspected.

Treatment

At the first sign of a hemolytic reaction, *stop the transfusion immediately.* Depending on the nature of the patient's reaction, prepare to:

- monitor vital signs every 15 to 30 minutes, watching for signs of shock
- maintain a patent I.V. line with normal saline solution; insert an indwelling catheter and monitor intake and output
- cover the patient with blankets to ease chills, and explain what's happening
- deliver supplemental oxygen at low flow rates through a nasal cannula or bag-valvemask (handheld resuscitation bag)
- give drugs as ordered: an I.V. antihypotensive drug and normal saline solution to combat shock, epinephrine to treat dyspnea and wheezing, diphenhydramine to combat cellular histamine released from mast cells, corticosteroids to reduce inflammation, and mannitol or furosemide to maintain urinary function. Administer parenteral antihistamines and corticosteroids for allergic reactions. (Severe reactions such as anaphylaxis may require epinephrine.) Administer antipyretics for nonhemolytic febrile reactions and appropriate I.V. antibiotics for bacterial contamination.

Special considerations

- Remember to fully document the transfusion reaction on the patient's chart, noting the transfusion's duration, the amount of blood absorbed, and a complete description of the reaction and of any interventions.

PREVENTION

Make sure you know your hospital's policy about giving blood before you give a transfusion. Then make sure you have the right blood and the right patient. Check and doublecheck the patient's name, hospital number, ABO blood group, and Rh status. If you find even a small discrepancy, don't give the blood. Notify the blood bank immediately and return the unopened unit.

AUTOIMMUNITY

Rheumatoid arthritis

A chronic, systemic, inflammatory disease, rheumatoid arthritis (RA) primarily attacks peripheral joints and surrounding muscles, tendons, ligaments, and blood vessels. Spontaneous remissions and unpredictable exacerbations mark the course of this potentially crippling disease. RA usually requires lifelong treatment and, sometimes, surgery. In most patients, the disease follows an intermittent course and allows normal activity, although 10% suffer total disability from severe articular deformity, associated extra-articular symptoms, or both. The prognosis worsens with the development of nodules, vasculitis, and high titers of rheumatoid factor (RF).

Causes and incidence

RA occurs worldwide, striking three times more females than males. Although it can occur at any age, it begins most often between ages 25 and 55. This disease affects more than 7 million people in the United States alone.

What causes the chronic inflammation characteristic of RA isn't known, but various theories point to infectious, genetic, and endocrine factors.

Currently, it's believed that a genetically susceptible individual develops abnormal or altered immunoglobulin (Ig) G antibodies when exposed to an antigen. This altered IgG antibody isn't recognized as “self,” and the individual forms an antibody against it — an antibody known as RF. By aggregating into complexes, RF generates inflammation. Eventually, cartilage damage by inflammation triggers additional immune responses, including activation of complement. This in turn attracts polymorphonuclear leukocytes and stimulates release of inflammatory mediators, which enhance joint destruction.

Much more is known about the pathogenesis of RA than about its causes. If unarrested, the inflammatory process within the joints occurs in four stages. First, synovitis develops from congestion and edema of the synovial membrane and joint capsule. Formation of pannus — thickened layers of granulation tissue — marks the second stage's onset. Pannus covers and invades cartilage and eventually destroys the joint capsule and bone. Progression to the third stage is characterized by fibrous ankylosis — fibrous invasion of the pannus and scar formation that occludes the joint space. Bone atrophy and malalignment cause visible deformities and disrupt the articulation of opposing bones, causing muscle atrophy and imbalance and, possibly, partial dislocations or subluxations. In the fourth stage, fibrous tissue calcifies, resulting in bony ankylosis and total immobility.

Complications

- Fibrous or bony ankylosis
- Soft tissue contractures
- Joint deformities
- Subluxations
- Carpal tunnel syndrome
- Popliteal (Baker's) cysts
- Osteoporosis
- Vasculitis
- Amyloidosis

- Cardiac and pulmonary disorders

Signs and symptoms

RA usually develops insidiously and initially produces nonspecific signs and symptoms, such as fatigue, malaise, anorexia, persistent low-grade fever, weight loss, lymphadenopathy, and vague articular symptoms. Later, more specific localized articular symptoms develop, commonly in the fingers at the proximal interphalangeal, metacarpophalangeal, and metatarsophalangeal joints. These symptoms usually occur bilaterally and symmetrically and may extend to the wrists, knees, elbows, and ankles. The affected joints stiffen after inactivity, especially upon rising in the morning. The fingers may assume a spindle shape from marked edema and joint congestion. The joints become tender and painful, at first only when the patient moves them, but eventually even at rest. They commonly feel hot to the touch. Ultimately, joint function is diminished.

Deformities are common if active disease continues. Proximal interphalangeal joints may develop flexion deformities or become hyperextended. Metacarpophalangeal joints may swell dorsally, and volar subluxation and stretching of tendons may pull the fingers to the ulnar side (“ulnar drift”). The fingers may become fixed in a characteristic “swan's neck” appearance, or “boutonnière” deformity. The hands appear foreshortened, the wrists boggy; carpal tunnel syndrome from synovial pressure on the median nerve causes tingling paresthesia in the fingers.

The most common extra-articular finding is the gradual appearance of rheumatoid nodules — subcutaneous, round or oval, nontender masses — usually on pressure areas such as the elbows. Vasculitis can lead to skin lesions, leg ulcers, and multiple systemic complications. Peripheral neuropathy may produce numbness or tingling in the feet or weakness and loss of sensation in the fingers. Stiff, weak, or painful muscles are common. Other common extra-articular effects include pericarditis, pulmonary nodules or fibrosis, pleuritis, scleritis, and episcleritis.

Another complication is destruction of the odontoid process, part of the second cervical vertebra. Rarely, cord compression may occur, particularly in patients with long-standing deforming disease. Upper

motor neuron signs and symptoms, such as a positive Babinski's sign and muscle weakness, may also develop.

RA can also cause temporomandibular joint disease, which impairs chewing and causes earaches. Other extra-articular findings may include infection, osteoporosis, myositis, cardiopulmonary lesions, lymphadenopathy, and peripheral neuritis.

Diagnosis

Typical clinical features suggest this disorder, but a definitive diagnosis is based on laboratory and other test results:

- X-rays — in early stages, show bone demineralization and soft-tissue swelling; later, loss of cartilage and narrowing of joint spaces; finally, cartilage and bone destruction and erosion, subluxations, and deformities
- Rheumatoid factor test — positive in 75% to 80% of patients as indicated by a titer of 1:160 or higher
- Synovial fluid analysis — reveals increased volume and turbidity but decreased viscosity and complement (C3 and C4) levels; white blood cell count usually exceeds 10,000/µl
- Erythrocyte sedimentation rate — elevated in 85% to 90% of patients (may be useful to monitor response to therapy because elevation commonly parallels disease activity)
- Complete blood count — usually reveals moderate anemia and slight leukocytosis.

CLASSIFYING RHEUMATOID ARTHRITIS

The criteria established by the American College of Rheumatology allow for the classification of rheumatoid arthritis.

Guidelines

A patient who meets four of the seven criteria is classified as having rheumatoid arthritis. He must experience the first four criteria for at least 6 weeks, and

a physician must observe the second through fifth criteria.

A patient with two or more other clinical diagnoses can also be diagnosed with rheumatoid arthritis.

Criteria

- Morning stiffness in and around the joints that lasts for 1 hour before full improvement.
- Arthritis in three or more joint areas, with at least three joint areas (as observed by a physician) exhibiting soft tissue swelling or joint effusions, not just bony overgrowth (the 14 possible areas involved include the right and left proximal interphalangeal, metacarpophalangeal, wrist, elbow, knee, ankle, and metatarsophalangeal joints)
- Arthritis of hand joints, including the wrist, the metacarpophalangeal joint, or the proximal interphalangeal joint
- Arthritis that involves the same joint area on both sides of the body
- Subcutaneous rheumatoid nodules over bony prominences
- Demonstration of abnormal amounts of serum rheumatoid factor by any method that produces a positive result in less than 5% of patients without rheumatoid arthritis
- Radiographic changes, usually on posterioanterior hand and wrist X-rays; these changes must show erosions or unequivocal bony decalcification localized in or most notably adjacent to the involved joints.

A C-reactive protein test can help monitor response to therapy.

The criteria for classifying rheumatoid arthritis developed by the American College of Rheumatology can also serve as guidelines for establishing a diagnosis. However, keep in mind that failure to meet these criteria—particularly early in the disease— doesn't exclude the diagnosis. (See *Classifying rheumatoid arthritis.*)

Treatment

Salicylates, particularly aspirin, are the mainstay of RA therapy because they decrease inflammation and relieve joint pain. Other useful medications include nonsteroidal anti-inflammatory drugs (such as indomethacin, fenoprofen, and ibuprofen), antimalarials (hydroxychloroquine), gold salts, penicillamine, and corticosteroids (prednisone). Immunosuppressants, such as cyclophosphamide, methotrexate, and azathioprine, are also therapeutic and are being used more commonly in early disease. (See *Drug therapy for arthritis*, pages 456 and 457.)

Supportive measures include 8 to 10 hours of sleep every night, frequent rest periods between daily activities, and splinting to rest inflamed joints. A physical therapy program including range-of-motion exercises and carefully individualized therapeutic exercises forestalls joint function loss; application of heat relaxes muscles and relieves pain. Moist heat usually works best for patients with chronic disease. Ice packs are effective during acute episodes.

DRUG THERAPY FOR ARTHRITIS

Drug and adverse effects	Clinical considerations
Aspirin	
Prolonged bleeding time; GI disturbances, including anorexia, nausea, dyspepsia, ulcers, and hemorrhage; hypersensitivity reactions ranging from urticaria to anaphylaxis; salicylism (mild toxicity: tinnitus, dizziness; moderate toxicity: restlessness, hyperpnea, delirium, marked lethargy; and severe toxicity: coma, seizures, severe hyperpnea)	▪ Don't use in patients with GI ulcers, bleeding, or hypersensitivity or in neonates. ▪ Tell the patient to take the drug with food, milk, antacid, or a large glass of water to reduce GI adverse effects.

	▪ Monitor the patient's salicylate level. Remember that toxicity can develop rapidly in febrile, dehydrated children. ▪ Teach the patient to reduce the dose, one tablet at a time, if tinnitus occurs. ▪ Teach the patient to watch for signs of bleeding, such as bruising, melena, and petechiae.
Fenoprofen, ibuprofen, naproxen, piroxicam, sulindac, and tolmetin	
Prolonged bleeding time; central nervous system abnormalities (headache, drowsiness, restlessness, dizziness, and tremor); GI disturbances, including hemorrhage and peptic ulcer; increased blood urea nitrogen and liver enzyme levels	▪ Tell the patient taking NSAIDs that he may have a higher risk of having a heart attack or stroke than those not taking NSAIDs. ▪ Don't use in patients with renal disease, in patients with asthma who have nasal polyps, or in children. ▪ Use cautiously in patients with GI and cardiac disease or if a patient is allergic to other nonsteroidal anti-inflammatory drugs (NSAIDs). ▪ Tell the patient to take the drug with milk or meals to reduce GI adverse effects. ▪ Tell the patient that the drug effect may be delayed for 2 to 3 weeks. ▪ Monitor the patient's kidney, liver, and auditory functions in long-term therapy. Stop the drug if abnormalities develop. ▪ Use cautiously in elderly patients; they may experience severe GI bleeding without warning.

Hydroxychloroquine and sulfasalazine	
Blood dyscrasias, GI irritation, corneal opacities, and keratopathy or retinopathy	▪ Don't use in patients with retinal or visual field changes. ▪ Use cautiously in patients with hepatic disease, alcoholism, glucose-6-phosphate dehydrogenase deficiency, or psoriasis. ▪ Perform complete blood count (CBC) and liver function tests before therapy and during chronic therapy. The patient should also have regular ophthalmologic examinations. ▪ Tell the patient to take the drug with food or milk to minimize GI adverse effects. ▪ Warn the patient that dizziness may occur.
Gold (oral and parenteral)	
Dermatitis, pruritus, rash, stomatitis, nephrotoxicity, blood dyscrasias and, with oral form, GI distress and diarrhea	▪ Watch for and report adverse effects. Observe for nitritoid reaction (flushing, fainting, and sweating). ▪ Check the patient's urine for blood and albumin before giving each dose. If positive, hold the drug and notify the physician. Stress to the patient the need for regular follow-up, including blood and urine testing. ▪ To avoid local nerve irritation, mix the drug well and give it via a deep I.M. injection in the buttock. ▪ Advise the patient not to expect improvement for 3 to 6 months.

	▪ Tell the patient to report rash, bruising, bleeding, hematuria, or oral ulcers.
Methotrexate	
Tubular necrosis, bone marrow depression, leukopenia, thrombocytopenia, pulmonary interstitial infiltrates, hyperuricemia, stomatitis, rash, pruritus, dermatitis, alopecia, diarrhea, dizziness, cirrhosis, and hepatic fibrosis	▪ Don't give to women who are pregnant or breast-feeding or to patients who are alcoholic. ▪ Monitor the patient's uric acid levels, CBC, and intake and output. ▪ Warn the patient to report any unusual bleeding (especially GI) or bruising promptly. ▪ Warn the patient to avoid alcohol, aspirin, and NSAIDs. ▪ Advise the patient to follow the prescribed regimen.
Abatacept	
Headache, dizziness, hypertension, nasopharyngitis, GI disturbances, including dyspepsia, nausea; UTI; back pain; respiratory system disturbances including upper respiratory infection, cough, exacerbation of COPD; skin rash; infusionrelated hypersensitivity reactions, infections, malignancy	▪ Don't give live vaccines during therapy and for 3 months following the end of treatment as it may decrease immune response to vaccine ▪ Use cautiously in patients with active infections, history or chronic infection, COPD or in women who are pregnant ▪ Patients who test positive for tuberculosis should be treated prior to using abatacept ▪ Contraindicated in patients taking a tumor necrosis antagonist (TNF)
Note: Other drugs that may be used in resistant cases include prednisone, chloroquine, azathioprine, and cyclophosphamide.	

Advanced disease may require synovectomy, joint reconstruction, or total joint arthroplasty.

Useful surgical procedures in RA include metatarsal head and distal ulnar resectional arthroplasty, insertion of a Silastic prosthesis between the metacarpophalangeal and proximal interphalangeal joints, and arthrodesis

(joint fusion). Arthrodesis sacrifices joint mobility for stability and pain relief. Synovectomy (removal of destructive, proliferating synovium, usually in the wrists, knees, and fingers) may halt or delay the course of this disease. Osteotomy (the cutting of bone or excision of a wedge of bone) can realign joint surfaces and redistribute stresses. Tendons may rupture spontaneously, requiring surgical repair. Tendon transfers may prevent deformities or relieve contractures. (See *When arthritis requires surgery*.)

Special considerations

- Assess all joints carefully. Look for deformities, contractures, immobility, and inability to perform everyday activities.
- Monitor the patient's vital signs and note weight changes, sensory disturbances, and level of pain. Administer analgesics as ordered and watch for adverse effects.
- Provide meticulous skin care. Check for rheumatoid nodules as well as pressure ulcers and breakdowns due to immobility, vascular impairment, corticosteroid treatment, or improper splinting. Use lotion or cleansing oil, not soap, for dry skin.
- Explain all diagnostic tests and procedures. Tell the patient to expect multiple blood samples to allow firm diagnosis and accurate monitoring of therapy.
- Monitor the duration, not the intensity, of morning stiffness because duration more accurately reflects the disease's severity. Encourage the patient to take hot showers or baths at bedtime or in the morning to reduce the need for pain medication.

- Apply splints carefully and correctly. Observe for pressure ulcers if the patient is in traction or wearing splints.
- Explain the nature of the disease. Make sure the patient and his family understand that RA is a chronic disease that requires major changes in lifestyle. Emphasize that there are no miracle cures, despite claims to the contrary.
- Encourage a balanced diet, but make sure the patient understands that special diets won't cure RA. Stress the need for weight control because obesity adds further stress to joints.
- Urge the patient to perform activities of daily living (ADLs), such as practicing good hygiene and dressing and feeding himself. Suggest ADL aids, such as a long-handled shoehorn; elastic shoelaces; zipper-pulls; button hooks; easy-to-handle cups, plates, and silverware; elevated toilet seats; and battery-operated toothbrushes. Household cleaning devices such as long-handled dustpans are also available. Patients who have trouble maneuvering fingers into gloves should wear mittens.
- ADLs that can be done in a sitting position should be encouraged. Allow the patient enough time to calmly perform these tasks.
- Provide emotional support. Remember that the patient with chronic illness easily becomes depressed, discouraged, and irritable. Encourage the patient to discuss his fears concerning dependency, sexuality, body image, and self-esteem. Refer him to an appropriate social service agency as needed.
- Discuss sexual aids: alternative positions, pain medication, and moist heat to increase mobility.
- Before discharge, make sure the patient knows how and when to take prescribed medication and how to recognize possible adverse effects.
- Teach the patient how to stand, walk, and sit correctly: upright and erect. Tell him to sit in chairs with high seats and armrests; he'll find it easier to get up from a chair if his knees are lower than his hips. If he doesn't own a chair with a high seat, recommend putting blocks of wood under a favorite chair's legs. Suggest an elevated toilet seat.
- Mobility aids are very helpful. Many medical and commercial stores offer assistive and supportive devices that promote self-care,

including an overhead grasping trapeze to get out of bed, easy-to-open drawers, handheld shower nozzles, handrails, and grab bars.

- Instruct the patient to pace daily activities, resting for 5 to 10 minutes out of each hour and alternating sitting and standing tasks. Adequate sleep and correct sleeping posture are important. He should sleep on his back on a firm mattress and should

avoid placing a pillow under his knees, which encourages flexion deformity.

- Teach the patient to avoid putting undue stress on joints and to use the largest joint available for a given task, to support weak or painful joints as much as possible, to avoid positions of flexion and promote positions of extension, to hold objects parallel to the knuckles as briefly as possible, to always use his hands toward the center of his body, and to slide — not lift — objects whenever possible. Enlist the aid of the occupational

therapist to teach how to simplify activities and protect arthritic joints. Stress the importance of shoes with proper support.

- Refer the patient to the Arthritis Foundation for more information on coping with the disease.

WHEN ARTHRITIS REQUIRES SURGERY

Arthritis severe enough to warrant total knee or total hip arthroplasty calls for comprehensive preoperative teaching and postoperative care.

Before surgery

- Explain preoperative and surgical procedures. Show the patient the prosthesis to be used if available.
- Teach the patient postoperative exercises such as isometrics and supervise his practice. Also, teach deep-breathing and coughing exercises that will be necessary after surgery.
- Explain that total hip or knee arthroplasty requires frequent range-of-motion exercises of the leg after

surgery; total knee arthroplasty requires frequent leg-lift exercises.

- Show the patient how to use a trapeze to move himself about in bed after surgery, and make sure he has a fracture bedpan handy.
- Tell the patient what kind of dressings to expect after surgery. After total knee arthroplasty, the patient's knee may be placed in a constant-passive-motion device to increase postoperative mobility and prevent emboli. After total hip arthroplasty, he'll have an abduction pillow between the legs to help keep the hip prosthesis in place.

After surgery

- Closely monitor and record vital signs. Watch for complications, such as steroid crisis and shock in patients receiving steroids. Monitor distal leg pulses often, marking them with a water-proof marker to make them easier to find.
- As soon as the patient awakens, have him do active dorsiflexion; if he can't, report this immediately. Supervise isometric exercises every 2 hours. After total hip arthroplasty, check traction for pressure areas and keep the bed's head raised between 30 and 45 degrees.
- Change or reinforce dressings, as needed, using sterile technique. Check wounds for hematoma, excessive drainage, color changes, or foul odor — all possible signs of hemorrhage or infection. (Wounds on rheumatoid arthritis patients may heal slowly.) Avoid contaminating dressings while helping the patient use the urinal or bedpan.
- Administer blood replacement products, antibiotics, and pain medication, as ordered. Monitor serum electrolyte

and hemoglobin levels and hematocrit.

- Have the patient turn, cough, and deep-breathe every 2 hours; then percuss his chest.
- After total knee arthroplasty, keep the patient's leg extended and slightly elevated.
- After total hip arthroplasty, keep the patient's hip in abduction to prevent dislocation by using such measures as a wedge pillow. Prevent external rotation and avoid hip flexion greater than 90 degrees. Watch for and immediately report any inability to rotate the hip or bear weight on it, increased pain, or a leg that appears shorter — all may indicate dislocation.
- As soon as allowed, help the patient get out of bed and sit in a chair, keeping his weight on the unaffected side. When he's ready to walk, consult with the physical therapist for walking instruction and aids.

ELDER TIP

Reinforce safety precautions for elderly patients, such as the removal of throw rugs and the use of handrails and adequate night lighting. Recommend a step stool for elderly patients who need to reach in overhead cupboards. Suggest that the patient purchase medication without safety caps, if available, because these caps can be difficult to open. Medication administration should be designed to follow a standard regimen that fits with the patient's lifestyle.

Juvenile rheumatoid arthritis

Affecting children younger than age 16, juvenile rheumatoid arthritis (JRA) is an inflammatory disorder of the connective tissues, characterized by joint swelling and pain or tenderness. It may also

involve organs such as the skin, heart, lungs, liver, spleen, and eyes, producing extra-articular signs and symptoms.

JRA has three major types: systemic (Still's disease or acute febrile type), polyarticular, and pauciarticular. Depending on the type, this disease can occur as early as age 6 weeks — although rarely before 6 months — with peaks of onset at ages 1 to 3 and 8 to 12.

The prognosis for JRA is generally good, although disabilities can occur. Long periods of spontaneous remission are common. Improvement or remission may occur at puberty.

Causes and incidence

The cause of JRA remains puzzling. Research continues to test several theories, such as those linking the disease to genetic factors or to an abnormal immune response. Viral or bacterial (particularly streptococcal) infection, trauma, and emotional stress may be precipitating factors, but their relationship to JRA remains unclear.

Considered the major chronic rheumatic disorder of childhood, JRA affects an estimated 50 to 100 per 100,000 children in the United States; overall incidence is twice as high in females, with variation among the types of JRA.

Complications

- Ocular damage
- Loss of vision
- Growth disturbances

Signs and symptoms

Signs and symptoms vary with the type of JRA. Affecting boys and girls almost equally, *systemic JRA* accounts for about 10% of cases. The affected children may have mild, transient arthritis or frank polyarthritis with fever and rash. Joint involvement may not be evident at first, but the child's behavior may clearly suggest joint pain. Such a child may constantly want to sit in a flexed position, may not walk much, or may

refuse to walk at all. Young children with JRA are noticeably irritable and listless.

Fever in systemic JRA occurs suddenly and spikes to 103° F (39.4° C) or higher once or twice daily, usually in the late afternoon, then rapidly returns to normal or subnormal. (This “sawtooth” or intermittent spiking fever pattern helps differentiate JRA from other inflammatory disorders.) When fever spikes, an evanescent rheumatoid rash commonly appears, consisting of small pale or salmon pink macules, usually on the trunk and proximal extremities and occasionally on the face, palms, and soles. Massaging or applying heat intensifies this rash. It's usually most conspicuous where the skin has been rubbed or subjected to pressure such as the areas of skin covered by underclothing.

Other signs and symptoms of systemic JRA may include hepatosplenomegaly, lymphadenopathy, pleuritis, pericarditis, myocarditis, and nonspecific abdominal pain.

Polyarticular JRA accounts for about 40% of cases and is three times more common in females than in males; affected children may be seronegative or seropositive

for rheumatoid factor (RF). It involves five or more joints and usually develops insidiously. Most commonly involved joints are the wrists, elbows, knees, ankles, and small joints of the hands and feet. Polyarticular JRA can also affect larger joints, including the temporomandibular joints, cervical spine, hips, and shoulders. These joints become swollen, tender, and stiff. Usually, the arthritis is symmetrical; it may be remittent or indolent. The patient may run a low-grade fever with daily peaks. Listlessness and weight loss can occur, possibly with lymphadenopathy and hepatosplenomegaly. Other signs of polyarticular JRA include subcutaneous nodules on the elbows or heels and noticeable developmental retardation.

Seropositive polyarticular JRA, the more severe type, usually occurs late in childhood and can cause destructive arthritis that mimics adult rheumatoid arthritis.

Pauciarticular JRA involves few joints (usually no more than four), typically affecting the knees and other large joints. This form accounts for 50% of cases and has major subtypes. The first, pauciarticular JRA

with chronic iridocyclitis, most commonly strikes females younger than age 6 and involves the knees, elbows, ankles, or iris. Inflammation of the iris and ciliary body is commonly asymptomatic but may produce pain, redness, blurred vision, and photophobia.

The second subtype, pauciarticular JRA with sacroiliitis, usually strikes males (9:1) older than age 8, who tend to test positive for human leukocyte antigen (HLA)-B27. This subtype is characterized by lower extremity arthritis that produces hip, sacroiliac, heel, and foot pain as well as Achilles' tendinitis. These patients may later develop the sacroiliac and lumbar arthritis characteristic of ankylosing spondylitis. Some also experience acute iritis, but not as many as those with the first subtype.

The third subtype includes patients with joint involvement who are antinuclear antibody (ANA) and HLA-B27 negative and don't develop iritis. These patients have a better prognosis than those with the first or second subtype.

Common to all types of JRA is joint stiffness in the morning or after periods of inactivity. Back pain and limited range of motion is common. Growth disturbances may also occur, resulting in uneven length of arms or legs due to overgrowth or undergrowth adjacent to inflamed joints.

Diagnosis

Persistent joint pain and the rash and fever clearly point to JRA. Laboratory tests are useful for ruling out other inflammatory or even malignant diseases that can mimic JRA. Disease activity and response to therapy can also be monitored through laboratory results.

- Complete blood count shows decreased hemoglobin levels, neutrophilia, and thrombocytosis.
- Erythrocyte sedimentation rate and C-reactive protein, haptoglobin, immunoglobulin, and C3 complement levels may be elevated.
- ANA test may be positive in patients who have pauciarticular JRA with chronic iridocyclitis.
- RF is present in 15% of JRA cases, compared with 85% of rheumatoid arthritis cases.

- Positive HLA-B27 antigens may forecast later development of ankylosing spondylitis.
- X-rays in early stages reveal changes, including soft-tissue swelling, effusion, and periostitis in affected joints. Later, osteoporosis and accelerated bone growth may appear, followed by subchondral erosions, joint space narrowing, bone destruction, and fusion.

Treatment

Successful management of JRA usually involves administration of anti-inflammatory drugs, physical therapy, carefully planned nutrition and exercise, and regular eye examinations. Both child and parents must be involved in therapy.

Aspirin is the initial drug of choice, with dosage based on the child's weight. However, other nonsteroidal anti-inflammatory drugs (NSAIDs) may also be used. If these prove ineffective, gold salts, hydroxychloroquine, and penicillamine may be tried. Because of adverse effects, steroids are generally reserved for treatment of systemic complications, such as pericarditis or iritis,

that are resistant to NSAIDs. Corticosteroids and mydriatic drugs are commonly used for iridocyclitis. Low-dose cytotoxic drug therapy is currently being investigated.

Physical therapy promotes regular exercise to maintain joint mobility and muscle strength, thereby preventing contractures, deformity, and disability. Good posture, gait training, and joint protection are also beneficial. Splints help reduce pain, prevent contractures, and maintain correct joint alignment.

Surgery is usually limited to soft-tissue releases to improve joint mobility. Joint replacement is delayed until the child has matured physically and can handle vigorous rehabilitation.

Special considerations

- Parents and health care professionals should encourage the child to be as independent as possible and to develop a positive attitude toward school, social development, and vocational planning.

- Regular slit-lamp examinations help ensure early diagnosis and treatment of iridocyclitis. Children with pauciarticular JRA with chronic iridocyclitis should be checked every 3 months during periods of active disease and every 6 months during remissions.

Psoriatic arthritis

Psoriatic arthritis is a rheumatoid-like joint disease associated with psoriasis of nearby skin and nails. Although the arthritis component of this syndrome may be clinically indistinguishable from rheumatoid arthritis, the rheumatoid nodules are absent, and serologic tests for rheumatoid factor are negative. Psoriatic arthritis is usually mild, with intermittent flare-ups, but in rare cases may progress to crippling arthritis mutilans. This disease affects males and females equally; onset usually occurs between ages 30 and 35.

Causes and incidence

Evidence suggests that predisposition to psoriatic arthritis is hereditary; 20% to 50% of patients are human leukocyte antigen-B27 positive. However, onset is usually precipitated by streptococcal infection or trauma.

About 5% to 8% of patients with psoriasis develop psoriatic arthritis. It occurs in up to 1% of the general population.

Signs and symptoms

Psoriatic lesions usually precede the arthritic component; however, after the full syndrome is established, joint and skin lesions recur simultaneously. Arthritis may involve one joint or several joints symmetrically. Spinal involvement occurs in some patients. Peripheral joint involvement is most common in the distal interphalangeal joints of the hands, which have a characteristic sausage-like appearance. Nail changes include pitting, transverse ridges, onycholysis, keratosis, yellowing, and destruction. The patient may experience general malaise, fever, and eye involvement.

Diagnosis

Inflammatory arthritis in a patient with psoriatic skin lesions suggests psoriatic arthritis.

CONFIRMING DIAGNOSIS

X-rays confirm joint involvement and show:

- *erosion of terminal phalangeal tufts*
- *"whittling" of the distal end of the terminal phalanges*
- *"pencil-in-cup" deformity of the distal interphalangeal joints*
- *relative absence of osteoporosis*
- *sacroiliitis*
- *atypical spondylitis with syndesmophyte formation. Hyperostosis and paravertebral ossification result, which may lead to vertebral fusion.*

Blood studies indicate negative rheumatoid factor and elevated erythrocyte sedimentation rate and uric acid levels.

Treatment

In mild psoriatic arthritis, treatment is supportive and consists of immobilization through bed rest or splints, isometric exercises, paraffin baths, heat therapy, and aspirin and other nonsteroidal anti-inflammatory drugs. Some patients respond well to low-dose systemic corticosteroids; topical steroids may help control skin lesions. Gold salts and, most commonly, methotrexate therapy are effective in treating both the articular and cutaneous effects of psoriatic arthritis. Antimalarials are contraindicated because they can provoke exfoliative dermatitis.

Special considerations

- Explain the disease and its treatment to the patient and his family.
- Encourage exercise, particularly swimming, to maintain strength and range of motion.

- Teach the patient how to apply skin care products and medications correctly; explain possible adverse effects.
- Stress the importance of adequate rest and protection of affected joints.
- Encourage regular, moderate exposure to the sun.
- Refer the patient to the Arthritis Foundation for self-help and support groups.

Ankylosing spondylitis

A chronic, usually progressive inflammatory disease, ankylosing spondylitis primarily affects the sacroiliac, apophyseal, and costovertebral joints, along with adjacent soft tissue. The disease (also known as rheumatoid spondylitis and Marie-Strümpell disease) usually begins in the sacroiliac joints and gradually progresses to the spine's lumbar, thoracic, and cervical regions. Deterioration of bone and cartilage can lead to fibrous tissue formation with eventual fusion of the spine or peripheral joints.

Ankylosing spondylitis may be equally prevalent in both sexes. Progressive disease is well recognized in men, but the diagnosis is commonly overlooked or missed in females, who tend to have more peripheral joint involvement.

Causes and incidence

Evidence strongly suggests a familial tendency in ankylosing spondylitis. The presence of human leukocyte antigen (HLA)-B27 (positive in more than 90% of patients with this disease) and circulating immune complexes suggests immunologic activity.

One out of 10,000 people has ankylosing spondylitis. It affects more males than females and usually emerges between ages 20 and 40, although it may develop in children younger than age 10.

Complication

- Atlantoaxial subluxation

Signs and symptoms

The first indication of ankylosing spondylitis is intermittent low back pain that's usually most severe in the morning or after a period of inactivity. Other signs and symptoms depend on the disease stage and may include:

- hip deformity and associated limited range of motion
- kyphosis in advanced stages, caused by chronic stooping to relieve symptoms
- mild fatigue, fever, anorexia, or weight loss; occasional iritis; aortic insufficiency and cardiomegaly; and upper lobe pulmonary fibrosis (mimics tuberculosis)
- pain and limited expansion of the chest due to involvement of the costovertebral joints
- peripheral arthritis involving shoulders, hips, and knees
- stiffness and limited motion of the lumbar spine
- tenderness over the inflammation site.

These signs and symptoms progress unpredictably, and the disease can go into remission, exacerbation, or arrest at any stage.

Diagnosis

Typical symptoms, family history, and the presence of HLA-B27 strongly suggest ankylosing spondylitis.

CONFIRMING DIAGNOSIS

Confirmation requires these characteristic X-ray findings:

- *blurring of the bony margins of joints in the early stage*
- *bilateral sacroiliac involvement*
- *patchy sclerosis with superficial bony erosions*
- *eventual squaring of vertebral bodies*
- *bamboo spine with complete ankylosis.*

Erythrocyte sedimentation rate and alkaline phosphatase and serum immunoglobulin A levels may be elevated. A negative rheumatoid factor helps rule out rheumatoid

arthritis, which produces similar symptoms.

Treatment

No treatment reliably stops progression of this disease, so management aims to delay further deformity through good posture, stretching and deep-breathing exercises and, in some patients, braces and light-weight supports. Anti-inflammatory analgesics, such as aspirin, indomethacin, sulfasalazine, and sulindac, control pain and inflammation.

Tumor necrosis factor inhibitors have been shown to improve symptoms. Corticosteroid therapy or medication to suppress the immune system may be prescribed to control various symptoms. Cytotoxic drugs that block cell growth have been used in patients who don't respond well to corticosteroids or those who are dependent on high doses of corticosteroids.

Severe hip involvement usually necessitates surgical hip replacement. Severe spinal involvement may require a spinal wedge osteotomy to separate and reposition the vertebrae. This surgery is performed only on selected patients because of the risk of spinal cord damage and the long convalescence involved.

Special considerations

Ankylosing spondylitis can be an extremely painful and crippling disease, so your main responsibility is to promote the patient's comfort. When dealing with such a patient, keep in mind that limited range of motion makes simple tasks difficult. Offer support and reassurance.

- Administer medications as ordered. Apply local heat and provide massage to relieve pain. Assess mobility and degree of discomfort frequently. Teach and assist with daily exercises as needed to maintain strength and function. Stress the importance of maintaining good posture.

- If treatment includes surgery, provide good postoperative care. Because ankylosing spondylitis is a chronic, progressively crippling condition, a comprehensive treatment plan should also reflect counsel from a social worker, visiting nurse, and dietitian.
- To minimize deformities, advise the patient to:

  – avoid any physical activity that places undue stress on the back such as lifting heavy objects

  – stand upright; to sit upright in a high, straight chair; and to avoid leaning over a desk

  – sleep in a prone position on a hard mattress and to avoid using pillows under neck or knees

  – avoid prolonged walking, standing, sitting, or driving

  – perform regular stretching and deep-breathing exercises and to swim regularly, if possible

  – have height measured every 3 to 4 months to detect any tendency toward kyphosis

  – seek vocational counseling if work requires standing or prolonged sitting at a desk

  – contact the local Arthritis Foundation chapter for a support group.

Sjögren's syndrome

The second most common autoimmune rheumatic disorder after rheumatoid arthritis (RA), Sjögren's syndrome is characterized by diminished lacrimal and salivary gland secretion (sicca complex). Sjögren's syndrome may be a primary disorder or it may be associated with connective tissue disorders, such as RA, scleroderma, systemic lupus erythematosus, and polymyositis. In some patients, the disorder is limited to the exocrine glands (glandular Sjögren's syndrome); in others, it also involves other organs, such as the lungs and kidneys (extraglandular Sjögren's syndrome).

Causes and incidence

The cause of Sjögren's syndrome is unknown, but genetic and environmental factors probably contribute to its development. Viral or bacterial infection or perhaps exposure to pollen may trigger Sjögren's syndrome in a genetically susceptible individual. Tissue damage results from infiltration by lymphocytes or from the deposition of immune complexes.

Lymphocytic infiltration may be classified as benign, malignant, or pseudolymphoma (nonmalignant, but tumorlike aggregates of lymphoid cells).

This syndrome occurs mainly in females (90% of patients); mean age of onset is 40 to 50 years of age.

Complications

- Corneal ulceration
- Deafness
- Renal tubular necrosis
- Splenomegaly

Signs and symptoms

About 50% of patients with Sjögren's syndrome have confirmed RA and a history of slowly developing sicca complex. However, some patients seek medical help for rapidly progressive and severe oral and ocular dryness, in many cases accompanied by periodic parotid gland enlargement. Ocular dryness (xerophthalmia) leads to foreign body sensation (gritty, sandy eye), redness, burning, photosensitivity, eye fatigue, itching, and mucoid discharge. The patient may also complain of a film across his field of vision.

Oral dryness (xerostomia) leads to difficulty swallowing and talking; abnormal taste or smell sensation or both; thirst; ulcers of the tongue, buccal mucosa, and lips (especially at the corners of the mouth); and severe dental caries. Dryness of the respiratory tract leads to epistaxis, hoarseness, chronic nonproductive cough, recurrent otitis media, and increased incidence of respiratory infections.

Other effects may include dyspareunia and pruritus (associated with vaginal dryness), generalized itching, fatigue, recurrent low-grade fever, and arthralgia or myalgia. Lymph node enlargement may be the first sign of malignant lymphoma or pseudolymphoma.

Specific extraglandular findings in Sjögren's syndrome include interstitial pneumonitis; interstitial nephritis, which results in renal tubular acidosis in 25% of patients; Raynaud's phenomenon (20%); and vasculitis, usually limited to the skin and characterized by palpable purpura on the legs (20%). About 50% of patients show signs of hypothyroidism related to autoimmune thyroid disease. A few patients develop systemic necrotizing vasculitis.

Diagnosis

Diagnosis of Sjögren's syndrome rests on the detection of two of the following three conditions: xerophthalmia, xerostomia (with salivary gland biopsy showing lymphocytic infiltration), and an associated autoimmune or lymphoproliferative disorder. Diagnosis must rule out other causes of oral and ocular dryness, including sarcoidosis, endocrine disorders, anxiety or depression, and effects of therapy such as radiation to the head and neck. More than 200 commonly used drugs also produce dry mouth as an adverse effect. In patients with salivary gland enlargement and severe lymphoid infiltration, diagnosis must rule out cancer.

Laboratory values include elevated erythrocyte sedimentation rate in most patients, mild anemia and leukopenia in 30%, and hypergammaglobulinemia in 50%. Autoantibodies are also common, including anti-Sjögren's syndrome-A (anti-Ro) and anti-Sjögren's syndrome-B (anti-La), which are antinuclear and antisalivary duct antibodies. From 75% to 90% of patients test positive for rheumatoid factor; 90%, for antinuclear antibodies.

Other tests help support this diagnosis. Schirmer's tearing test and slit-lamp examination with rose bengal dye are used to measure eye involvement. Salivary gland involvement is evaluated by measuring the volume of parotid saliva and by secretory sialography and salivary scintigraphy. Lower-lip biopsy shows salivary gland infiltration by lymphocytes.

Treatment

Treatment is usually symptomatic and includes conservative measures to relieve ocular or oral dryness. Mouth dryness can be relieved by using a methylcellulose swab or spray and by drinking plenty of fluids, especially at mealtime. Meticulous oral hygiene is essential, including regular flossing, brushing, at-home fluoride treatment, and frequent dental checkups.

Instill artificial tears as often as every half hour to prevent eye damage (corneal ulcerations and corneal opacifications) from insufficient tear secretions. Some patients may also benefit from instillation of an eye ointment at bedtime or from twicea-day use of sustained-release cellulose capsules (Lacrisert). If infection develops, antibiotics should be given immediately; topical steroids should be avoided. Other treatment measures vary with associated extraglandular findings. Parotid gland enlargement requires local heat and analgesics. Pulmonary and renal interstitial disease necessitate corticosteroid use. Accompanying lymphoma is treated with a combination of chemotherapy, surgery, or radiation.

Special considerations

- Stress the need to humidify home and work environments to help relieve respiratory dryness.
- Advise the patient to avoid drugs that decrease saliva production, such as atropine derivatives, antihistamines, anticholinergics, and antidepressants.
- If mouth lesions make eating painful, suggest high-protein, high-calorie liquid supplements to prevent malnutrition.
- Advise the patient to avoid sugar, which contributes to dental caries. Tobacco; alcohol; and spicy, salty, or highly acidic foods, which cause mouth irritation, should also be avoided.
- Suggest normal saline solution drops or aerosolized spray for nasal dryness.

- Advise the patient to avoid prolonged hot showers and baths and to use moisturizing lotions to help ease dry skin. Suggest K-Y lubricating jelly as a vaginal lubricant.
- Suggest the use of sunglasses to protect the patient's eyes from dust, wind, and strong light. Moisture chamber spectacles may also be helpful. Because dry eyes are more susceptible to infection, advise the patient to keep his face clean and to avoid rubbing his eyes.
- Refer the patient to the Sjögren's Syndrome Foundation for additional information and support.

Lupus erythematosus

A chronic inflammatory disorder of the connective tissues, lupus erythematosus appears in two forms. *Discoid lupus erythematosus* affects only the skin. (See *Discoid lupus erythematosus*.) *Systemic lupus erythematosus* (SLE) affects multiple organ systems as well as the skin and can be fatal. Like rheumatoid arthritis, SLE is characterized by recurring remissions and exacerbations, especially common during the spring and summer. The prognosis improves with early detection and treatment, but remains poor for patients who develop cardiovascular, renal, or neurologic complications or severe bacterial infections.

Causes and incidence

The exact cause of SLE remains a mystery, but evidence points to interrelated immunologic, environmental, hormonal, and genetic factors. Autoimmunity is thought to be the prime causative mechanism. In autoimmunity, the body produces antibodies against its own cells such as the antinuclear antibody. The formed antigen-antibody complexes can suppress the body's normal immunity and damage tissues. Patients with SLE produce antibodies against many different tissue components, such as red blood cells (RBCs), neutrophils, platelets, lymphocytes, or almost any organ or tissue in the body.

Certain predisposing factors may make a person susceptible to SLE. Physical or mental stress, streptococcal or viral infections, exposure to sunlight or ultraviolet light, immunization, pregnancy, and abnormal estrogen metabolism may all affect this disease's development.

SLE may also be triggered or aggravated by treatment with certain drugs — for example, procainamide, hydralazine, anticonvulsants and, less commonly, penicillins, sulfa drugs, and hormonal contraceptives.

SLE strikes 9 times more women than men, increasing to 15 times more during childbearing years. It occurs worldwide but is most prevalent among Asians and Blacks.

Complications

- Pleurisy

- Pleural effusions
- Pneumonitis
- Pulmonary hypertension
- Pericarditis
- Endocarditis
- Coronary atherosclerosis
- Renal failure

DISCOID LUPUS ERYTHEMATOSUS

Discoid lupus erythematosus (DLE) is a form of lupus erythematosus marked by chronic skin eruptions that, if untreated, can lead to scarring and permanent disfigurement. About 1 of 20 patients with DLE later develops systemic lupus erythematosus (SLE). The exact cause of DLE is unknown, but some evidence suggests an autoimmune defect. An estimated 60% of patients with DLE are women in their late 20s or older. This disease is rare in children.

DLE lesions are raised, red, scaling plaques, with follicular plugging and central atrophy. The raised edges and sunken centers give them a coinlike appearance. Although these lesions can appear anywhere on the body,

they usually erupt on the face, scalp, ears, neck, and arms or on any part of the body that's exposed to sunlight. Such lesions can resolve completely or may cause hypopigmentation or hyperpigmentation, atrophy, and scarring. Facial plaques sometimes assume the butterfly pattern characteristic of SLE. Hair tends to become brittle or may fall out in patches.

As a rule, patient history and the appearance of the rash itself are diagnostic. Lupus erythematosus cell test is positive in fewer than 10% of patients. Skin biopsy of lesions reveals immunoglobulins or complement components. SLE must be ruled out.

Patients with DLE should avoid prolonged exposure to the sun, fluorescent lighting, or reflected sunlight. They should wear protective clothing, use sunscreening agents, avoid engaging in outdoor activities during periods of most intense sunlight (between 10 a.m. and 2 p.m.), and report any changes in the lesions. Drug treatment consists of topical, intralesional, or systemic medication, as in SLE.

Signs and symptoms

The onset of SLE may be acute or insidious and produces no characteristic clinical pattern. However, its symptoms commonly include fever, weight loss, malaise, and fatigue as well as rashes and polyarthralgia. SLE may involve every organ system. In 90% of patients, joint involvement is similar to that in rheumatoid arthritis. Skin lesions are most commonly erythematous rashes in areas exposed to light. The classic butterfly rash over the nose and cheeks occurs in fewer than 50% of the patients. (See *Butterfly rash*, page 468.) Ultraviolet rays often provoke or aggravate skin eruptions. Vasculitis can develop (especially in the digits), possibly leading to infarctive lesions, necrotic leg ulcers, or digital gangrene. Raynaud's phenomenon appears in about 20% of

patients. Patchy alopecia and painless ulcers of the mucous membranes are common.

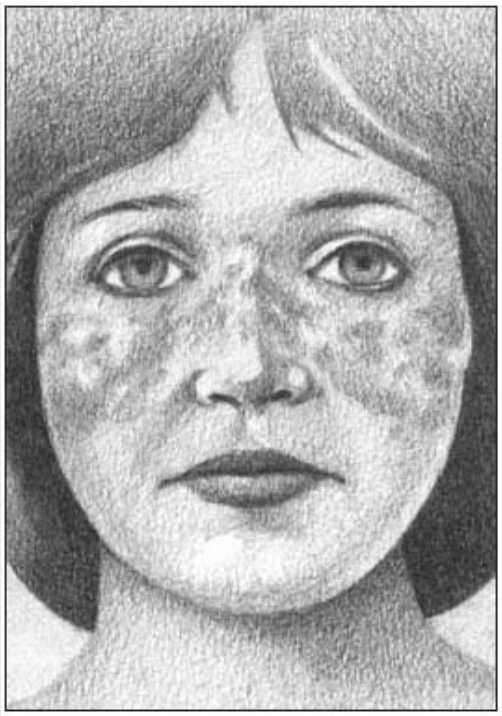
Constitutional symptoms of SLE include aching, malaise, fatigue, low-grade or spiking fever, chills, anorexia, and weight loss. Lymph node enlargement (diffuse or local, and nontender), abdominal pain, nausea, vomiting, diarrhea, and constipation may occur. Females may experience irregular menstrual periods or amenorrhea during the active phase of SLE.

About 50% of SLE patients develop signs of cardiopulmonary abnormalities, such as pleuritis, pericarditis, and dyspnea. Myocarditis, endocarditis, tachycardia, parenchymal infiltrates, and pneumonitis may occur. Renal effects may include hematuria, proteinuria, urine sediment, and cellular casts, which may progress to total kidney failure. Urinary tract infections

may result from heightened susceptibility to infection. Seizure disorders and mental dysfunction may indicate neurologic damage. Central nervous system (CNS) involvement may produce emotional instability, psychosis, and organic mental syndrome. Headaches, irritability, and depression are common. (See *Signs of systemic lupus erythematosus*.)

BUTTERFLY RASH

In the classic butterfly rash, lesions appear on the cheeks and the bridge of the nose, creating a characteristic butterfly pattern. The rash may vary in severity from malar erythema to discoid lesions (plaque).



Diagnosis

Diagnostic tests for patients with SLE include a complete blood count with differential (for signs of anemia and decreased white blood cell [WBC] count); platelet count (may be decreased); erythrocyte sedimentation rate (commonly elevated); and serum electrophoresis (may show hypergammaglobulinemia).

Specific tests for SLE include:

- antinuclear antibody panel, including anti-deoxyribonucleic acid (DNA) and anti-Smith antibodies — generally positive for lupus alone. (Because the anti-DNA test is rarely positive in other conditions, it's the most specific test for SLE. However, if the patient is in remission, anti-DNA may be reduced or absent [correlates with disease activity, especially renal involvement, and helps monitor response to therapy]. Other tests may be performed as needed to rule out other disorders.)
- urine studies — may show RBCs and WBCs, urine casts and sediment, and significant protein loss (more than 0.5 g/24 hours)
- blood studies — decreased serum complement (C3 and C4) levels indicate active disease

- chest X-ray — may show pleurisy or lupus pneumonitis
- electrocardiogram — may show conduction defect with cardiac involvement or pericarditis
- kidney biopsy — determines disease stage and extent of renal involvement.

Some patients show a positive lupus anticoagulant test and a positive anticardiolipin test. Such patients are prone to antiphospholipid syndrome (thrombosis and thrombocytopenia).

Treatment

Patients with mild disease require little or no medication. Nonsteroidal anti-inflammatory drugs, including aspirin, control arthritis symptoms in many patients. Skin lesions need topical treatment. Corticosteroid creams are recommended for acute lesions.

Refractory skin lesions are treated with intralesional corticosteroids or antimalarials such as hydroxychloroquine. Because hydroxychloroquine can cause retinal damage, such treatment requires ophthalmologic examination every 6 months.

Corticosteroids remain the treatment of choice for systemic symptoms of SLE, for acute generalized exacerbations, or for serious disease related to vital organ systems, such as pleuritis, pericarditis, lupus nephritis, vasculitis, and CNS involvement. Initial doses equivalent to 60 mg or more of prednisone often bring noticeable improvement within 48 hours. As soon as symptoms are under control, steroid dosage is tapered slowly. (Rising serum complement levels and decreasing anti-DNA titers indicate patient response.) Diffuse proliferative glomerulonephritis, a major complication of SLE, requires treatment with large doses of steroids. If renal failure occurs, dialysis or kidney transplant may be necessary. In some patients, cytotoxic drugs may delay or prevent deteriorating renal status. Antihypertensive drugs and dietary changes may also be warranted in renal disease.

The photosensitive patient should wear protective clothing (hat, sunglasses, long sleeves, and slacks) and use a screening agent, with a sun protection factor of at least 15, when outdoors. Because SLE usually

strikes females of childbearing age, questions about pregnancy commonly arise. Available evidence indicates that a woman with SLE can have a safe, successful pregnancy if she has no serious renal or neurologic impairment.

Special considerations

Careful assessment, supportive measures, emotional support, and patient education are all important parts of the care plan for patients with SLE.

- Watch for constitutional symptoms: joint pain or stiffness, weakness, fever, fatigue, and chills. Observe for dyspnea, chest pain, and any edema of the extremities. Note the size, type, and location of skin lesions. Check urine for hematuria, scalp for hair loss, and skin and mucous membranes for petechiae, bleeding, ulceration, pallor, and bruising.
- Provide a balanced diet. Renal involvement may mandate a low-sodium, low-protein diet.
- Urge the patient to get plenty of rest. Schedule diagnostic tests and procedures to allow adequate rest. Explain all tests and procedures. Tell the patient that several blood samples are needed initially, then periodically, to monitor progress.
- Apply heat packs to relieve joint pain and stiffness. Encourage regular exercise to maintain full range of motion (ROM) and prevent contractures. Teach ROM exercises as well as body alignment and postural techniques. Arrange for physical therapy and occupational counseling as appropriate.
- Explain the expected benefit of prescribed medications. Watch for adverse effects, especially when the patient is taking high doses of corticosteroids.
- Advise the patient receiving cyclophosphamide to maintain adequate hydration. If prescribed, give mesna to prevent hemorrhagic cystitis and ondansetron to prevent nausea and vomiting.
- Monitor vital signs, intake and output, weight, and laboratory reports. Check pulse rates and observe for orthopnea. Check stools and GI secretions for blood.

- Observe for hypertension, weight gain, and other signs of renal involvement.
- Assess for signs of neurologic damage: personality change, paranoid or psychotic behavior, ptosis, or diplopia. Take seizure precautions. If Raynaud's phenomenon is present, warm and protect the patient's hands and feet.
- Offer cosmetic tips such as suggesting the use of hypoallergenic makeup and refer the patient to a hairdresser who specializes in scalp disorders.

- Advise the patient to purchase medications in quantity, if possible. Warn against “miracle” drugs for relief of arthritis symptoms.
- Refer the patient to the Lupus Foundation of America and the Arthritis Foundation as needed.

SIGNS OF SYSTEMIC LUPUS ERYTHEMATOSUS

Diagnosing systemic lupus erythematosus (SLE) is difficult because SLE commonly mimics other diseases; symptoms may be vague and vary greatly from patient to patient.

The revised criteria for SLE must include four or more of the following signs:

- abnormal titer of antinuclear antibody
- hemolytic disorder
- malar rash
- discoid rash
- arthritis
- oral ulcerations
- photosensitivity
- serositis
- renal disorder
- neurologic disorder

- immunologic disorder.

Fibromyalgia syndrome

Fibromyalgia syndrome (FMS) previously called fibrositis, is a diffuse pain syndrome and one of the most common causes of chronic musculoskeletal pain. It's characterized by diffuse musculoskeletal pain, daily fatigue, and poor-quality sleep, along with multiple tender points on examination (in specific areas). More women than men are affected, and although FMS may occur at almost any age, the peak incidence is in patients between ages 20 and 60.

FMS has also been reported in children, who have more diffuse pain and a higher incidence of sleep disturbances than adult patients. They may have fewer tender points and typically improve after 2 to 3 years of follow-up.

Causes and incidence

The cause of FMS is unknown, but it may be a primary disorder or occur in association with an underlying disease, such as systemic lupus erythematosus, rheumatoid arthritis, osteoarthritis, and sleep apnea syndrome.

The pain is located mainly in muscle areas, but no distinct abnormalities have been documented on microscopic evaluation of biopsies of tender points when compared with normal muscle. One theory suggests that blood flow to the muscle is decreased (because of poor muscle aerobic conditioning, rather than other physiologic abnormalities); another suggests blood flow tin the thalamus and caudate nucleus is decreased, leading to a lowered pain threshold. Still other theories suggest that the cause lies in endocrine dysfunction, such as abnormal pituitary-adrenal axis responses, or in abnormal levels of the neurotransmitter serotonin in brain centers, which affect pain and sleep. Abnormal functioning of other pain-processing pathways may also be involved.

Considerable overlap of symptoms with other pain syndromes, such as chronic fatigue syndrome, raises the question of association with infection with microbes, such as parvovirus B19.

The development of FMS may be multifactorial and influenced by stress (physical and mental), physical conditioning, poor-quality sleep, neuroendocrine factors, psychiatric factors and possibly, hormonal factors (explaining the predominance in women).

Signs and symptoms

The primary symptoms is diffuse, dull, aching pain that's typically concentrated across the neck and shoulders and in the lower back and proximal limbs. It can involve all body quadrants (bilateral upper trunk and arms, and bilateral lower trunk and legs) and typically is worse in the morning, when it's associated with stiffness. The pain can vary form day to day and be exacerbated by stress, lack of sleep, weather changes, and inactivity.

Sleep disturbance and fatigue are commonly reported. The patient awakens feeling fatigued and remains so throughout the day. Fatigue is commonly present from a half hour to several hours after rising in the morning and can last for the rest of the day.

Other associated features that can occur with FMS include irritable bowel syndrome, tension headaches, puffy hands (sensation of hand swelling, especially in the morning), and paresthesia.

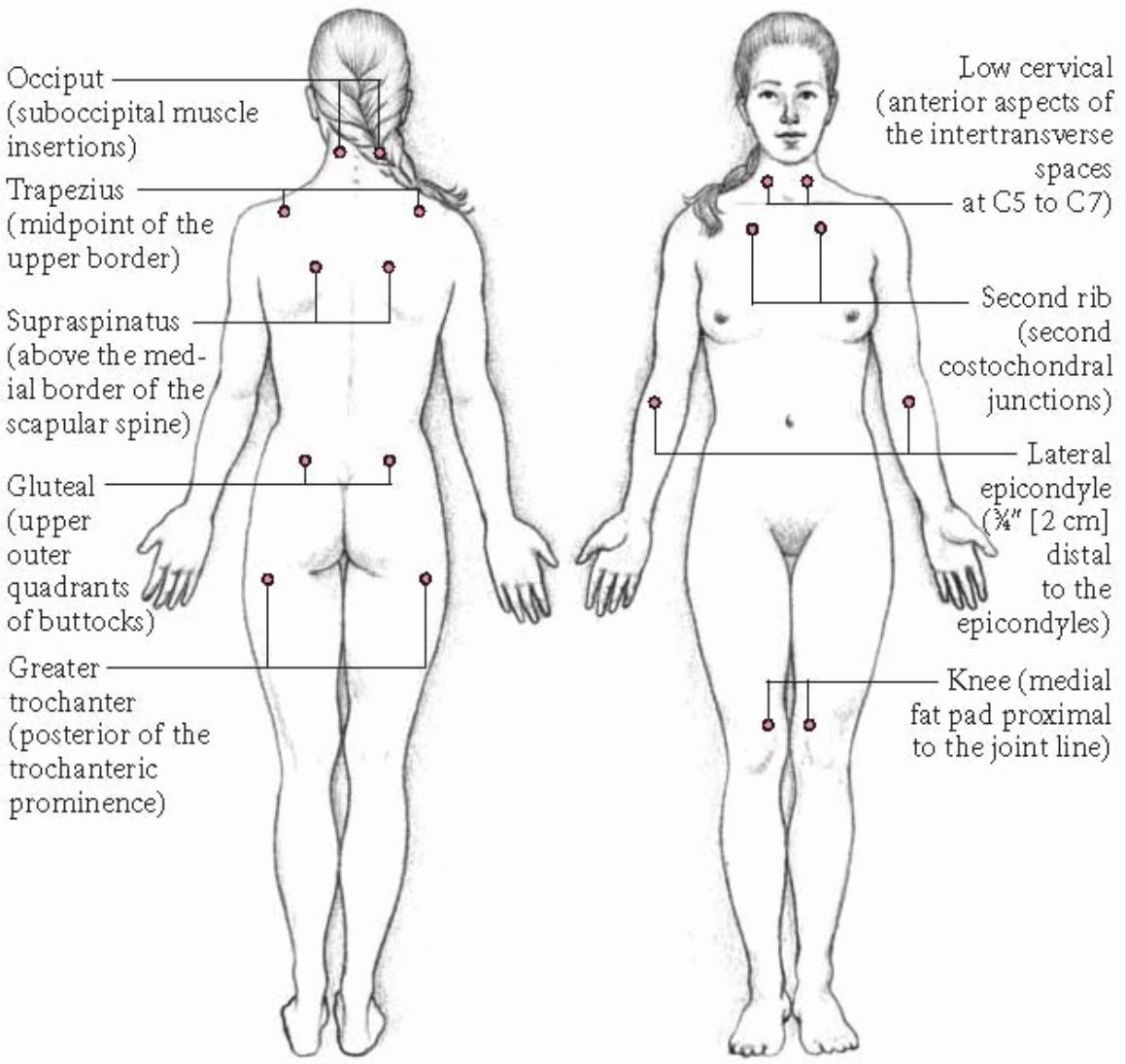
Diagnosis

FMS is diagnosed in a patient with characteristic symptoms, multiple tender points on examination and exclusion of other illnesses that can cause similar features. Tender points are elicited by applying a moderate amount of pressure to specific location. This examination can be fairly subjective, but many FMS patients with true tender points wince or withdraw when pressure is applied at a certain intensity. Nontender control points can also be tested to assess for conversion reactions (psychogenic rheumatism), in which patients

hurt everywhere or exhibit other psychosomatic illnesses. (See *Tender points of fibromyalgia*.)

TENDER POINTS OF FIBROMYALGIA

The patient with fibromyalgia may report specific areas of tenderness. These areas are indicated in the illustrations below.



Treatment

Drugs, such as amitriptyline and nortriptyline, are typically used to improve sleep and control pain. Nonsteroidal anti-inflammatory drugs (NSAIDS) and corticosteroids are typically ineffective against FMS pain. An opioid to control chronic pain of FMS should be used only with extreme caution, preferably under the guidance of a pain specialist.

A physical therapist may assist in the management of FMS through the use of education, injection of tender points, massage therapy, and ultrasound treatments for particular problem areas. In a few studies, acupuncture, phototherapy, and mindbody exercises (such as yoga and tai chi) have been somewhat beneficial.

Special considerations

- The most important aspect of FMS management is patient education. Patients must understand that although FMS pain can be severe and is often chronic, the syndrome

  is common and doesn't lead to deforming or life-threatening complications.
- A regular, low-impact aerobic exercise can be effective in improving the patient's muscle conditioning, energy level, and overall sense of well-being. The FMS patient should be taught preexercise and postexercise stretching to minimize injury. Strongly encourage a low-intensity exercise program, such as walking, bicycling, or swimming, and to increase level of intensity as tolerated.

Goodpasture's syndrome

In Goodpasture's syndrome, hemoptysis and rapidly progressive glomerulonephritis follow the deposition of antibody against the alveolar and glomerular basement membrane (GBM). The prognosis improves with aggressive immunosuppressive and antibiotic therapy along with dialysis or renal transplantation.

Causes and incidence

The cause of Goodpasture's syndrome is unknown. Although some cases have been associated with exposure to hydrocarbons or type 2 influenza, many have no precipitating events. The high incidence of human leukocyte antigen DRW2 in these patients suggests a genetic predisposition. Abnormal production and deposition of antibody against GBM and alveolar basement membrane activate the complement and inflammatory responses, resulting in glomerular and alveolar tissue damage.

This syndrome may occur at any age but is most common in men between ages 20 and 30. A second peak incidence occurs between ages 50 and 70, with men and women in this age group affected equally.

Complications

- Renal failure
- Pulmonary edema and hemorrhage

Signs and symptoms

Goodpasture's syndrome may initially cause malaise, fatigue, and pallor associated with severe iron deficiency anemia. Pulmonary findings range from slight dyspnea and cough with blood-tinged sputum to hemoptysis and frank pulmonary hemorrhage. Subclinical pulmonary bleeding may precede overt hemorrhage and renal disease by months or years. Usually, renal findings are subtler, although some patients note hematuria and peripheral edema.

Diagnosis

CONFIRMING DIAGNOSIS

Confirmation of Goodpasture's syndrome requires measurement of circulating anti-GBM antibody by radioimmunoassay and linear staining of GBM and alveolar basement membrane by immunofluorescence.

Immunofluorescence of alveolar basement membrane shows linear deposition of immunoglobulin as well as complement 3 and fibrinogen. Immunofluorescence of GBM also shows linear deposition of immunoglobulin combined with detection of circulating anti-GBM antibody. This finding distinguishes Goodpasture's from other pulmonary-renal syndromes, such as Wegener's granulomatosis, polyarteritis, and systemic lupus erythematosus.

A lung biopsy reveals interstitial and intra-alveolar hemorrhage with hemosiderin-laden macrophages. Chest X-ray reveals pulmonary

infiltrates in a diffuse, nodular pattern, and renal biopsy commonly shows focal necrotic lesions and cellular crescents.

Creatinine and blood urea nitrogen (BUN) levels typically increase two to three times normal. Urinalysis may reveal red blood cells and cellular casts, which typify glomerular inflammation. Granular casts and proteinuria may also be observed.

Treatment

Treatment aims to remove antibody by plasmapheresis and to suppress antibody production with immunosuppressive drugs, such as cyclophosphamide, to stop attacks by immune cells on the kidneys and lungs. Patients with renal failure may benefit from dialysis or transplantation. Aggressive ultrafiltration helps relieve pulmonary edema that may aggravate pulmonary hemorrhage. High-dose I.V. steroids also help control pulmonary hemorrhage.

Special considerations

- Promote adequate oxygenation by elevating the bed's head and administering humidified oxygen. Encourage the patient to conserve his energy. Assess respirations and breath sounds regularly; note sputum quantity and quality.
- Monitor vital signs, arterial blood gases, hematocrit, and coagulation studies.
- Transfuse blood and administer steroids as ordered. Observe closely for drug adverse effects.
- Assess renal function by monitoring symptoms, intake and output, daily weights, creatinine clearance, and BUN and creatinine levels.
- Tell the patient and his family what signs and symptoms to expect and how to relieve them. Carefully describe other treatment measures such as dialysis.

Reiter's syndrome

A self-limiting syndrome associated with polyarthritis (dominant feature), urethritis, balanitis (inflammation of the glans penis), conjunctivitis, and mucocutaneous lesions, Reiter's syndrome appears to be related to infection, either venereal or enteric.

Causes and incidence

The cause of Reiter's syndrome is unknown, but most cases follow venereal or enteric infection. Because 75% to 85% of patients with Reiter's syndrome test positive for the human leukocyte antigen (HLA)-B27, genetic susceptibility is likely. Reiter's syndrome has followed infections caused by *Campylobacter, Salmonella, Yersinia,* and *Chlamydia* organisms.

This disease usually affects young males (ages 20 to 40); it's rare in females and children. However, due to the uncertainty of diagnosis and variations in the definition of this disorder, incidence is estimated at approximately 3.5 per 100,000 people. About 1% to 3% of all patients with nonspecific urethritis develop an episode of arthritis.

Complications

- Chronic heel pain
- Ankylosing spondylitis
- Persistent joint pain and swelling

Signs and symptoms

The patient with Reiter's syndrome may complain of dysuria, hematuria, urgent and frequent urination, and mucopurulent penile discharge, with swelling and reddening of the urethral meatus. Small painless ulcers may erupt on the glans penis (balanitis). These coalesce to form irregular patches that cover the penis and scrotum. He may also experience suprapubic pain, fever, anorexia with weight loss, and other genitourinary (GU) complications, such as prostatitis and hemorrhagic cystitis.

Arthritic symptoms usually follow GU or enteric symptoms and last from 2 to 4 months. Asymmetrical and extremely variable polyarticular

arthritis is most common, with a tendency to develop in weight-bearing joints of the legs and sometimes in the low back or sacroiliac joints. The arthritis is usually acute, with warm, erythematous, and painful joints, but it may be mild, with minimal synovitis. Muscle wasting is common near affected joints. Fingers and toes may swell and appear sausagelike.

Ocular symptoms include mild bilateral conjunctivitis, possibly complicated by keratitis, iritis, retinitis, or optic neuritis. In severe cases, burning, itching, and profuse mucopurulent discharge are possible.

In 30% of patients, skin lesions (keratoderma blennorrhagicum) develop 4 to 6 weeks after onset of other symptoms and may last for several weeks. These macular to hyperkeratotic lesions commonly resemble those of psoriasis. They usually occur on the palms and soles but can develop anywhere on the trunk, extremities, or scalp. Nails become thick, opaque, and brittle; keratic debris accumulates under the nails. In many patients, painless, transient ulcerations erupt on the buccal mucosa, palate, and tongue.

Diagnosis

Nearly all patients with Reiter's syndrome test positive for HLA-B27 and have an elevated white blood cell (WBC) count and erythrocyte sedimentation rate. Mild anemia may develop. Urethral discharge and synovial fluid contain many WBCs, mostly

polymorphonuclear leukocytes. Synovial fluid is high in complement and protein and is grossly purulent. Cultures of discharge and synovial fluid rule out other causes such as gonococci.

During the first few weeks, X-rays are normal and may remain so, but some patients may show osteoporosis in inflamed areas. If inflammation persists, X-rays may show erosions of the small joints, periosteal proliferation (new bone formation) of involved joints, and calcaneal spurs.

Treatment

No specific treatment exists for Reiter's syndrome. Most patients recover in 2 to 16 weeks. About 50% of patients have recurring acute attacks,

whereas the rest follow a chronic course, experiencing continued synovitis and sacroiliitis. In acute stages, limited weight bearing or complete bed rest may be necessary.

Any underlying infection should be treated with antibiotics. Arthritis is treated with nonsteroidal anti-inflammatory agents and pain relievers. Local administration of corticosteroids may help relieve persistent inflammation in one joint. Physical therapy includes range-of-motion and strengthening exercises and the use of padded or supportive shoes to prevent contractures and foot deformities. Therapy to suppress the immune system may be considered in severe cases but is limited due to toxic adverse effects.

Special considerations

- Explain Reiter's syndrome. Discuss the medications and their possible adverse effects. Warn the patient to take medications with meals or milk to prevent GI bleeding.
- Encourage normal daily activity and moderate exercise. Suggest a firm mattress and encourage good posture and body mechanics.
- Arrange for occupational counseling if the patient has severe or chronic joint impairment.

Scleroderma

Scleroderma, also known as *systemic sclerosis,* is a diffuse connective tissue disease characterized by fibrotic, degenerative, and occasionally inflammatory changes in skin, blood vessels, synovial membranes, skeletal muscles, and internal organs (especially the esophagus, intestinal tract, thyroid, heart, lungs, and kidneys).

This disease can be classified as systemic (involving skin, blood vessels, and internal organs) or localized (limited to skin and tissues). Each classification has distinctive forms.

Systemic forms include:

- *limited cutaneous systemic sclerosis (or CREST syndrome)*—a benign form characterized by calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia

- *diffuse cutaneous systemic sclerosis*— characterized by generalized skin thickening and invasion of internal organs
- *systemic sine scleroderma*—a rare form of the disease, includes involvement of internal organs but does not have skin involvement.

Localized forms include:

- *morphea*—characterized by patchy skin changes with a droplike appearance
- *linear scleroderma*—characterized by a band of thickened skin on the face or extremities that severely damages underlying tissues, causing atrophy and deformity (most common in childhood).

Other forms include *chemically induced localized scleroderma, eosinophilia myalgia syndrome* (recently associated with ingestion of L-tryptophan), *toxic oil syndrome* (associated with contaminated oil), and *graft-versus-host disease*.

Causes and incidence

The cause of scleroderma is unknown. Risk factors include exposure to silica dust and polyvinyl chloride.

Scleroderma affects 300,000 people in the United States, more women than men, especially between ages 30 and 50. About 30% of patients with scleroderma die within 5 years of onset.

Complications

- Arrhythmias
- Dyspnea
- Malignant hypertension

Signs and symptoms

Scleroderma typically begins with Raynaud's phenomenon — blanching, cyanosis, and erythema of the fingers and toes in response to stress or

exposure to cold. Progressive phalangeal resorption may shorten the fingers.

Compromised circulation, which results from abnormal thickening of the arterial intima, may cause slowly healing ulcerations on the tips of the fingers or toes that may lead to gangrene. Raynaud's phenomenon may precede scleroderma by months or years.

Later symptoms include pain, stiffness, and finger and joint swelling. Skin thickening produces taut, shiny skin over the entire hand and forearm. Facial skin also becomes tight and inelastic, causing a masklike appearance and “pinching” of the mouth. As tightening progresses, contractures may develop.

GI dysfunction causes frequent reflux, heartburn, dysphagia, and bloating after meals. These symptoms may cause the patient to decrease food intake and lose weight. Other GI effects include abdominal distention, diarrhea, constipation, and malodorous floating stools.

Diagnosis

Typical cutaneous changes provide the first clue to diagnosis. Results of diagnostic tests include:

- blood studies—slightly elevated erythrocyte sedimentation rate, positive rheumatoid factor in 25% to 35% of patients, and positive antinuclear antibody test
- chest X-rays—bilateral basilar pulmonary fibrosis
- electrocardiogram—possible nonspecific abnormalities related to myocardial fibrosis
- GI X-rays—distal esophageal hypomotility and stricture, duodenal loop dilation, small-bowel malabsorption pattern, and large diverticula
- hand X-rays—terminal phalangeal tuft resorption, subcutaneous calcification, and joint space narrowing and erosion
- pulmonary function studies—decreased diffusion and vital capacity and restrictive lung disease

- skin biopsy—may show changes consistent with the disease's progress, such as marked thickening of the dermis and occlusive vessel changes
- urinalysis—proteinuria, microscopic hematuria, and casts (with renal involvement).

Treatment

Currently, no cure exists for scleroderma. Treatment aims to preserve normal body functions and minimize complications. Use of an immunosuppressant such as chlorambucil is a common palliative measure. Corticosteroids and colchicine seem to stabilize symptoms; D-penicillamine may be helpful. Blood platelet levels need to be monitored throughout drug therapy.

Other treatments vary according to symptoms:

- chronic digital ulcerations—a digital plaster cast to immobilize the area, minimize trauma, and maintain cleanliness; possibly surgical debridement
- esophagitis with stricture—antacids, cimetidine, periodic esophageal dilation, and a soft, bland diet
- hand debilitation—physical therapy to maintain function and promote muscle strength, heat therapy to relieve joint stiffness, and patient teaching to make performance of daily activities easier
- Raynaud's phenomenon—various vasodilators and antihypertensive agents (such as methyldopa or calcium channel blockers), intermittent cervical sympathetic blockade or, rarely, thoracic sympathectomy
- scleroderma kidney (with malignant hypertension and impending renal failure)— dialysis, antihypertensives, and calcium channel blockers
- small-bowel involvement (diarrhea, pain, malabsorption, and weight loss)— broad-spectrum antibiotics, such as erythromycin or tetracycline, to counteract bacterial overgrowth in the duodenum and jejunum related to hypomotility.

Special considerations

- Assess the patient's motion restrictions, pain, vital signs, intake and output, respiratory function, and daily weight.

- Because of compromised circulation, warn against finger-stick blood tests.
- Remember that air conditioning may aggravate Raynaud's phenomenon.
- Help the patient and his family adjust to the patient's new body image and to the limitations and dependence that these changes cause.
- Teach the patient to avoid fatigue by pacing activities and organizing schedules to include necessary rest.
- Stress to the patient and his family the need to accept the fact that this condition is incurable. Encourage them to express their feelings and help them cope with their fears and frustrations by offering information about the disease, its treatment, and relevant diagnostic tests.
- Whenever possible, let the patient participate in treatment by measuring his own intake and output, planning his own diet, assisting in dialysis, giving himself heat therapy, and doing prescribed exercises.
- Direct the patient to seek out support groups, which can be found in every state. Instruct the patient to call 1-800-722-HOPE or go to *www.scleroderma.org*.

Vasculitis

Vasculitis includes a broad spectrum of disorders characterized by inflammation and necrosis of blood vessels. Its clinical effects, which reflect tissue ischemia caused by blood flow obstruction, and confirming laboratory procedures depend on the vessels involved. The prognosis is variable. For example, hypersensitivity vasculitis is usually a benign disorder limited to the skin, but more extensive polyarteritis nodosa can be rapidly fatal. Vasculitis can occur at any age, except for mucocutaneous lymph node syndrome, which occurs only during childhood. Vasculitis may be a primary disorder or occur secondary to

other disorders, such as rheumatoid arthritis or systemic lupus erythematosus.

Causes and incidence

How vascular damage develops in vasculitis isn't well understood. It has been associated with a history of serious infectious disease, such as hepatitis B or bacterial endocarditis, and high-dose antibiotic therapy. Current theory holds that it's initiated by excessive circulating antigen, which triggers the formation of soluble antigen-antibody complexes. These complexes can't be effectively cleared by the reticuloendothelial system, so they're deposited in blood vessel walls (type III hypersensitivity). Increased vascular permeability associated with release of vasoactive amines by platelets and basophils enhances such deposition. The deposited complexes activate the complement cascade, resulting in chemotaxis of neutrophils, which release lysosomal enzymes. In turn, these enzymes cause vessel damage and necrosis, which may precipitate thrombosis, occlusion, hemorrhage, and ischemia.

Another mechanism that may contribute to vascular damage is the cell-mediated (T-cell) immune response. In this response, circulating antigen triggers the release of soluble mediators by sensitized lymphocytes, which attracts macrophages. The macrophages release intracellular enzymes, which cause vascular damage. They can also transform into the epithelioid and multinucleated giant cells that typify the granulomatous vasculitides. Phagocytosis of immune complexes by macrophages enhances granuloma formation.

Complications

- Renal failure
- Renal hypertension
- Glomerulitis
- Fibrous scarring of lung tissue
- Stroke
- GI bleeding
- Necrotizing vasculitis

- Spontaneous hemorrhage
- Intestinal obstruction
- Myocardial infarction
- Pericarditis
- Rupture or mesenteric aneurysms

Signs and symptoms

The clinical effects of vasculitis vary according to the blood vessels involved.

Diagnosis

Laboratory tests performed to confirm a diagnosis of vasculitis depend on the blood vessels involved. (See *Types of vasculitis*.)

TYPES OF VASCULITIS

Vasculitis occurs in various forms; diagnosis depends on the presenting signs and symptoms.

Type	Vessels involved	Signs and symptoms	Diagnosis
Polyarteritis nodosa	Small to medium arteries throughout the body (Lesions tend to be segmental, occur at bifurcations and branchings of arteries, and spread distally to arterioles. In severe cases, lesions	Hypertension, abdominal pain, myalgias, headache, joint pain, and weakness	History of symptoms; elevated erythrocyte sedimentation rate (ESR); and blood urea nitrogen and creatinine levels; leukocytosis; anemia; thrombocytosis; depressed C3 complement; rheumatoid factor more than 1:60; circulating immune complexes; tissue biopsy

	circumferentially involve adjacent veins.)		showing necrotizing vasculitis
Allergic angiitis and granulomatosis (Churg-Strauss syndrome)	Small to medium arteries (including arterioles, capillaries, and venules), mainly of the lungs, kidneys, but also other organs	Resembles polyarteritis nodosa with hallmark of severe pulmonary involvement	History of asthma; eosinophilia; increased immunoglobulin (IG)E level; tissue biopsy showing granulomatous inflammation with eosinophilic infiltration
Polyangiitis overlap syndrome (microscopic polyangitis)	Small to medium arteries (including arterioles, capillaries, and venules) of the lungs and other organs	Combines symptoms of polyarteritis nodosa, allergic angiitis, and granulomatosis	Possible history of allergy; eosinophilia; tissue biopsy showing granulomatous inflammation with eosinophilic infiltration
Wegener's granulomatosis	Medium to large; vessels of the respiratory tract and kidney; may also involve small arteries and veins	Fever, pulmonary congestion, cough, malaise, anorexia, weight loss, and mild to severe hematuria	Tissue biopsy showing necrotizing vasculitis with granulomatous inflammation; leukocytosis; elevated ESR and immunoglobulin (Ig) A and IgG levels; low titer rheumatoid factor; circulating immune complexes; antineutrophil cytoplasmic antibody in more than 90% of patients
Temporal arteritis (Giant cell arteritis)	Medium to large arteries, most commonly branches of the carotid artery	Fever, myalgia, jaw claudication, visual changes, and headache (associated	Decreased hemoglobin (Hb) level; elevated ESR; tissue biopsy showing panarteritis with infiltration of

		with polymyalgia rheumatica syndrome)	mononuclear cells, giant cells within vessel wall, fragmentation of internal elastic lamina, and proliferation of intima
Takayasu's arteritis (aortic arch syndrome)	Medium to large arteries, particularly the aortic arch, its branches and, possibly, the pulmonary artery	Malaise, pallor, nausea, night sweats, arthralgias, anorexia, weight loss, pain or paresthesia distal to affected area, bruits, loss of distal pulses, syncope and, if a carotid artery is involved, diplopia and transient blindness; may progress to heart failure or stroke	Decreased Hb level; leukocytosis; positive lupus erythematosus cell preparation and elevated ESR; arteriography showing calcification and obstruction of affected vessels; tissue biopsy showing inflammation of adventitia and intima of vessels, and thickening of vessel walls
Hypersensitivity vasculitis	Small vessels, especially of the skin	Palpable purpura, papules, nodules, vesicles, bullae, ulcers, or chronic or recurrent urticaria	History of exposure to antigen, such as a microorganism or drug; tissue biopsy showing leukocytoclastic angiitis, usually in postcapillary venules, with infiltration of polymorphonuclear leukocytes, fibrinoid necrosis, and extravasation of erythrocytes
Mucocutaneous lymph node syndrome (Kawasaki disease)	Small to medium vessels, primarily of the lymph nodes; may progress to involve coronary arteries	Fever; nonsuppurative cervical adenitis; edema; congested conjunctivae; erythema of oral cavity, lips, and palms; and desquamation of	History of symptoms; elevated ESR; tissue biopsy showing intimal proliferation and infiltration of vessel walls with mononuclear cells; echocardiography necessary

		fingertips; may progress to arthritis, myocarditis, pericarditis, myocardial infarction, and cardiomegaly	
Behçet's disease	Small vessels, primarily of the mouth and genitalia, but also of the eyes, skin, joints, GI tract, and central nervous system	Recurrent oral ulcers, eye lesions, genital lesions, and cutaneous lesions	History of symptoms
Henoch-Schöntein purpura	Any blood vessel in the skin	Red to purple papule skin lesions, pain, infarction, joint pain, numbness, weakness, fever, fatigue, dysmenorrhea, pyrosis, dysphonia, and dysphagia	History of symptoms, muscle biopsy, chest X-ray, and sedimentation rate

Treatment

Treatment of vasculitis aims to minimize irreversible tissue damage associated with ischemia. In primary vasculitis, treatment may involve removal of an offending antigen or use of anti-inflammatory or immunosuppressant drugs. For example, antigenic drugs, food, and other environmental substances should be identified and eliminated, if possible.

Drug therapy in primary vasculitis commonly involves low-dose cyclophosphamide (2 mg/kg orally daily) with daily corticosteroids. In rapidly fulminant vasculitis, cyclophosphamide dosage may be increased to 4 mg/kg daily for the first 2 to 3 days, followed by the regular dose. Prednisone should be given in a dose of 1 mg/kg/day in divided doses for

7 to 10 days, with consolidation to a single morning dose by 2 to 3 weeks. When the vasculitis appears to be in remission or when prescribed cytotoxic drugs take full effect, corticosteroids are tapered down to a single daily dose. Finally, an alternate-day schedule of steroids may continue for 3 to 6 months before slow discontinuation of steroids.

In secondary vasculitis, treatment focuses on the underlying disorder.

Special considerations

- Assess patients with Wegener's granulomatosis for dry nasal mucosa. Instill nose drops to lubricate the mucosa and help diminish crusting, or irrigate the nasal passages with warm normal saline solution.
- Monitor vital signs. Use a Doppler ultrasonic flowmeter, if available, to auscultate blood pressure in patients with Takayasu's arteritis, whose peripheral pulses are generally difficult to palpate.
- Monitor intake and output. Check daily for edema. Keep the patient well hydrated (3 L daily) to reduce the risk of hemorrhagic cystitis associated with cyclophosphamide therapy.
- Provide emotional support to help the patient and his family cope with an altered body image — the result of the disorder or its therapy. (For example, Wegener's granulomatosis may be associated with saddle nose, steroids may cause weight gain, and cyclophosphamide may cause alopecia.)
- Teach the patient how to recognize drug adverse effects. Monitor the patient's white blood cell count during cyclophosphamide therapy to prevent severe leukopenia.

Polymyositis and dermatomyositis

Diffuse, inflammatory myopathies of unknown cause, polymyositis and dermatomyositis produce symmetrical weakness of striated muscle — primarily proximal muscles of the shoulder and pelvic girdles, neck, and pharynx. In dermatomyositis, such muscle weakness is accompanied by cutaneous involvement. These diseases usually progress slowly, with frequent exacerbations and remissions. They occur in twice as many

females as males (except dermatomyositis with malignant tumor, which is most common in males older than age 40).

The prognosis usually worsens with age. Death commonly occurs from associated cancer, respiratory disease, or heart failure or from the adverse effects of drug therapy. On the other hand, 80% to 90% of affected children regain normal function with proper treatment. However, if untreated, childhood dermatomyositis may progress rapidly to disabling contractures and muscle atrophy.

Causes and incidence

Although the cause of polymyositis remains puzzling, researchers believe that it may result from an autoimmune reaction. Presumably, the patient's T cells inappropriately recognize muscle fiber antigens as foreign and attack muscle tissue, causing diffuse or focal muscle fiber degeneration. (Regeneration of new muscle cells then follows, producing remission.) Polymyositis and dermatomyositis may be associated with other disorders, such as allergic reactions; systemic lupus erythematosus (SLE); scleroderma; rheumatoid arthritis; Sjögren's syndrome; carcinomas of the lung, breast, or other organs; systemic viral infection; or D-penicillamine administration.

Annual incidence is 5 to 10 in 100,000 people.

Signs and symptoms

Polymyositis begins acutely or insidiously with muscle weakness, tenderness, and discomfort. It affects proximal muscles more than distal muscles and impairs performance of ordinary activities. The patient may have trouble getting up from a chair, combing his hair, reaching into a high cupboard, climbing stairs, or even raising his head from a pillow. Other muscular symptoms include inability to move against resistance, proximal dysphagia, dysphonia, and difficulty breathing.

In dermatomyositis, an erythematous rash usually erupts on the face, neck, upper back, chest, and arms as well as around the nail beds. A characteristic heliotropic rash appears on the eyelids, accompanied by periorbital edema. Gottron's papules (violet, flat-topped lesions) may appear on the interphalangeal joints.

Diagnosis

CONFIRMING DIAGNOSIS

Diagnosis requires a muscle biopsy that shows necrosis, degeneration, regeneration, and interstitial chronic lymphocytic infiltration. Magnetic resonance imaging and an electrocardiogram, as well as the use of electromyography, aid in diagnosis.

Other tests differentiate polymyositis from diseases that cause similar muscular or cutaneous symptoms, such as muscular dystrophy, advanced trichinosis, psoriasis, seborrheic dermatitis, and SLE.

Typical laboratory results in polymyositis include elevated erythrocyte sedimentation rate, elevated white blood cell count, and elevated muscle enzyme levels (creatine kinase, aldolase, and serum aspartate aminotransferase) not attributable to hemolysis of red blood cells or hepatic or other diseases. Other laboratory results include increased urine creatine level (more than 150 mg/24 hours), decreased creatinine level, and positive antinuclear antibodies. Electromyography shows polyphasic short-duration potentials, fibrillation (positive spike waves), and bizarre high-frequency repetitive changes.

Treatment

High-dose corticosteroid therapy relieves inflammation and lowers muscle enzyme levels. Within 2 to 6 weeks after treatment, serum muscle enzyme levels usually return to normal, and muscle strength improves, permitting a gradual tapering down of corticosteroid dosage. If the patient responds poorly to corticosteroids, treatment may include cytotoxic or immunosuppressant drugs. Supportive therapy includes bed rest during the acute phase, range-of-motion (ROM) exercises to prevent contractures, analgesics and application of heat to relieve painful muscle spasms, and diphenhydramine to relieve itching. Patients older than age 40 need thorough assessment for coexisting cancer.

Special considerations

- Assess level of pain, muscle weakness, and ROM daily. Give analgesics as needed.
- If the patient is confined to bed, prevent pressure ulcers by giving good skin care. To prevent footdrop and contractures, apply high-topped sneakers, and assist with passive ROM exercises at least four times daily. Teach the patient's family how to perform these exercises on the patient.
- If 24-hour urine collection for creatine or creatinine is necessary, make sure your coworkers understand the procedure. When you assist with muscle biopsy, make sure the biopsy isn't taken from an area of recent needle insertion.
- If the patient has a rash, warn him not to scratch, as it may cause infection. If antipruritic medication doesn't relieve severe itching, apply tepid sponges or compresses.
- Encourage the patient to feed and dress himself to the best of his ability but to ask for help when needed. Advise him to pace his activities to counteract muscle weakness. Encourage him to express his anxiety. Ease his fear of dependence by reassuring him that muscle weakness is probably temporary.
- Explain the disease to the patient and his family. Prepare them for diagnostic procedures and possible adverse effects of corticosteroid therapy (weight gain, hirsutism, hypertension, edema, amenorrhea, purplish striae, glycosuria, acne, and easy bruising). Advise a low-sodium diet to prevent fluid retention. Emphatically warn against abruptly discontinuing corticosteroids. Reassure the patient that steroidinduced weight gain will diminish when the drug is discontinued.

IMMUNODEFICIENCY

X-linked infantile hypogammaglobulinemia

X-linked infantile hypogammaglobulinemia is a recessive, congenital disorder in which all five immunoglobulins (Ig) — IgM, IgG, IgA, IgD, and

IgE — and circulating B cells are absent or deficient but T cells are intact. It's also called *Bruton's agammaglobulinemia* and *X-linked agammaglobulinemia*. Affecting males almost exclusively, this disorder causes severe, recurrent infections during infancy. Prognosis is good with early treatment, except in infants who develop polio or persistent viral infection. Infection usually causes some permanent damage, especially in the neurologic or respiratory system.

Causes and incidence

In this disease, B cells and B-cell precursors may be present in the bone marrow and peripheral blood, but a mutation in the B-cell protein tyrosine kinase keep B cells from maturing and secreting immunoglobulin. Without protective immunoglobulins, the affected person develops repeated infections. Worldwide, malnutrition is the primary cause of antibody disorders.

Humoral immune deficiencies account for 50% of all primary immunodeficiencies. IgA deficiency is the most common antibody deficiency symdrome, followed by common variable immunodeficiency (CVID). The incidence of these two disorders is 1 in 700 persons. Selective IgM deficiency is rare. IgG4 deficiency occurs in 10% to 15% of the population.

Complications

- Chronic otitis media
- Chronic sinusitis
- Encephalitis
- Failure to thrive
- Hepatitis
- Enteroviral infections
- Meningitis

Signs and symptoms

Typically, the infant with X-linked hypogammaglobulinemia is asymptomatic until age 6 months, when transplacental maternal immunoglobulins that provided immunity have been depleted. He then develops recurrent bacterial otitis media, pneumonia, dermatitis, bronchitis, and meningitis — usually caused by pneumococci, streptococci, *Haemophilus influenzae*, or other gram-negative organisms. Purulent conjunctivitis, abnormal dental caries, and polyarthritis resembling rheumatoid arthritis may also occur. Severe malabsorption associated with infestation by *Giardia lamblia* may retard development. Despite recurrent infections, lymphadenopathy and splenomegaly are usually absent.

Diagnosis

Diagnosis of X-linked hypogammaglobulinemia can be especially difficult because recurrent infections are common even in normal infants (many of whom don't start producing their own antibodies until age 18 to 20 months). Immunoelectrophoresis and quantitative immunoglobulins (nephelometry) confirm decreased levels, or a total absence, of IgM, IgA, and IgG in the serum. IgG is usually less than 200 mg/dl, and IgA and IgM are almost unmeasurable. However, diagnosis by this method usually isn't possible until the infant is 9 months old. Antigenic stimulation confirms an inability to produce specific antibodies, although cellular immunity remains intact.

Treatment

Treatment aims to prevent or control infections and to boost the patient's immune response. Injection of immune serum globulin (gamma globulin, IV Ig) helps maintain immune response. Because these injections are painful, give them deep into a large muscle mass, such as the gluteal or thigh muscles, and massage well. If the dosage is more than 1.5 ml, divide it and inject it into more than one site; for frequent injections, rotate the injection sites. Because immune globulin is composed primarily of IgG, the patient may also need fresh frozen plasma infusions to provide IgA and IgM. Mucosal secretory IgA can't be replaced by therapy, resulting in crippling pulmonary disease in many patients.

Judicious use of antibiotics also helps combat infection; in some cases, chronic broad-spectrum antibiotics may be indicated. During acute infection, monitor the patient closely. Maintain adequate nutrition and hydration. Perform chest physiotherapy if required.

Special considerations

- Carefully explain all treatment measures, and make sure the patient and his family understand the disorder.
- Teach the patient and his family how to recognize early signs of infection and counsel them to report such signs promptly. Advise them to have cuts and scrapes cleaned immediately. Warn them to avoid crowds and people who have active infections.
- Suggest genetic counseling if parents have questions about vulnerability of future offspring.

Common variable immunodeficiency

Common variable immunodeficiency is characterized by progressive deterioration of B-cell (humoral) immunity, resulting in increased susceptibility to infection. Unlike X-linked hypogammaglobulinemia, this disorder (also known as acquired hypogammaglobulinemia or agammaglobulinemia with immunoglobulin [Ig]-bearing B cells) usually causes symptoms after infancy and childhood, between ages 25 and 40. It affects males and females equally and usually doesn't interfere with normal life span or normal pregnancy and offspring.

Causes and incidence

The cause of common variable immunodeficiency is unknown. Most patients have a normal circulating B-cell count but defective synthesis or release of immunoglobulins. Many also exhibit progressive deterioration of T-cell (cell-mediated) immunity revealed by delayed hypersensitivity skin testing.

Complications

- Conjunctivitis
- Chronic sinusitis
- *Giardia lamblia* GI infection
- Upper and lower respiratory tract infections
- Encephalitis
- Meningitis
- Hemolytic anemia

Signs and symptoms

In common variable immunodeficiency, pyogenic bacterial infections are characteristic but tend to be chronic rather than acute (as in X-linked hypogammaglobulinemia). Recurrent sinopulmonary infections, chronic bacterial conjunctivitis, and malabsorption (commonly associated with infestation by *Giardia lamblia*) are usually the first clues to immunodeficiency.

Common variable immunodeficiency may be associated with autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, hemolytic anemia, and pernicious anemia, and with cancers, such as leukemia and lymphoma.

Diagnosis

Characteristic diagnostic markers in this disorder are decreased serum IgM, IgA, and IgG levels detected by immunoelectrophoresis, along with a normal circulating B-cell count. Antigenic stimulation confirms an inability to produce specific antibodies; cell-mediated immunity may be intact or delayed. X-rays usually show signs of chronic lung disease or sinusitis.

Treatment

Treatment and care of patients with common variable immunodeficiency are essentially the same as for those with X-linked hypogammaglobulinemia.

Injection of immune globulin (usually weekly to monthly) helps maintain the immune response. Because these injections are painful, give them deep into a large muscle mass, such as the gluteal or thigh muscles, and massage well. If the dosage is more than 1.5 ml, divide the dose and inject it into more than one site; for frequent injections, rotate the injection sites. Because immune globulin is composed primarily of IgG, the patient may also need fresh frozen plasma infusions to provide IgA and IgM.

Antibiotics are the mainstay for combating infection. Regular X-rays and pulmonary function studies help monitor lung infection; chest physiotherapy may be ordered to forestall or help clear such infection.

Special considerations

- Teach the patient and his family how to recognize early signs of infection and counsel them to report such signs promptly. Advise the patient to avoid crowds and people who have active infections.
- Stress the importance of good nutrition and regular follow-up care.

IgA deficiency

Total absence or severe deficiency of immunoglobulin (Ig) A, also known as *Janeway Type 3 dysgammaglobulinemia,* is the most common primary immunoglobulin deficiency, appearing in as many as 1 in 400 to 1,000 people. IgA — the major immunoglobulin in human saliva, nasal and bronchial fluids, and intestinal secretions — guards against bacterial and viral reinfections. Consequently, IgA deficiency leads to chronic sinopulmonary infections, allergies, chronic diarrhea, GI diseases, and other disorders. The prognosis is good for patients who receive correct treatment, especially if they have no associated disorders.

Causes and incidence

IgA deficiency seems to be linked to autosomal dominant or recessive inheritance. The disorder has familial trends and occurs frequently in immediate relatives of individuals with common variable immunodeficiency. The presence of normal numbers of peripheral blood lymphocytes carrying IgA receptors and of normal amounts of other

immunoglobulins suggests that B cells may not be secreting IgA, as they haven't matured into IgA-producing plasma cells. Congenital intrauterine infection with rubella, toxoplasmosis, or cytomegalovirus can result in selective IgA deficiency. Treatment for seizures with phenytoin and hydantoin, as well as Wilson's disease (an inherited disorder treated with penicillamine), can result in temporarily acquired selective IgA deficiency. When the medications are stopped, the IgA level returns to normal. Some drugs such as anticonvulsants may cause transient IgA deficiency.

Signs and symptoms

Some IgA-deficient patients have no symptoms, possibly because they have extra amounts of low-molecular-weight IgM. This immunoglobulin takes over IgA function and helps maintain immunologic defenses. Among patients who develop symptoms, chronic sinopulmonary infection is the most common. Other effects are respiratory allergy, often triggered by infection; GI tract diseases, such as celiac disease, ulcerative colitis, and regional enteritis; autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, immunohemolytic anemia, and chronic hepatitis; and malignant tumors, such as squamous cell carcinoma of the lungs, reticulum cell sarcoma, and thymoma.

Age of onset varies. Some IgA-deficient children with recurrent respiratory disease and middle ear inflammation may begin to synthesize IgA spontaneously as recurrent infections subside and their condition improves.

Diagnosis

Serum immunoelectrophoresis and quantitative immunologic analyses of patients with IgA-deficiency show serum IgA levels below 7 mg/dl. Although IgA is usually absent from secretions in patients with IgA-deficiency, levels may be normal in rare cases. IgE is normal, whereas IgM may be normal or elevated in serum and secretions. Normally absent low-molecular-weight IgM may be present.

Tests may also indicate autoantibodies and antibodies against IgG (rheumatoid factor), IgM, and bovine milk. Cell-mediated immunity and

secretory piece (the glycopeptide that transports IgA) are usually normal, and most circulating B cells appear normal.

Treatment

Selective IgA deficiency has no known cure. Treatment aims to control symptoms of associated diseases, such as respiratory and GI infections, and is generally the same as for a patient with normal IgA.

ALERT

Don't give an IgA-deficient patient immune globulin (IV Ig) because sensitization may lead to anaphylaxis during future administration of blood products.

If transfusion with blood products is necessary, minimize the risk of adverse reaction by using washed red blood cells or avoid the reaction completely by cross-matching the patient's blood with that of an IgA-deficient donor.

Special considerations

Because this is a lifelong disorder, teach the patient to prevent infection, to recognize its early signs, and to seek treatment promptly.

DiGeorge syndrome

DiGeorge syndrome, also called *congenital thymic hypoplasia or aplasia,* is a disorder characterized by the partial or total absence of cell-mediated immunity that results from a deficiency of T lymphocytes. It typically produces life-threatening hypocalcemia that may be associated with cardiovascular and facial anomalies. Patients seldom live beyond age 2 without a fetal thymus transplant; the prognosis improves when this transplant, correction of hypocalcemia, and repair of cardiac anomalies are possible.

Causes and incidence

DiGeorge syndrome is probably caused by abnormal fetal development (12th week of gestation) of the third and fourth pharyngeal pouches, which interferes with thymus formation. As a result, the thymus is

completely absent or partially present in an abnormal location, causing deficient T cell-mediated immunity. (See *Role of the thymus in immune response*.) This syndrome has been associated with maternal alcoholism and resultant fetal alcohol syndrome.

Complications

- Hypocalcemia (life-threatening)
- Seizures
- Central nervous system damage
- Failure to thrive
- Anorexia
- Diarrhea
- Weight loss
- Cardiac failure

Signs and symptoms

Symptoms are usually obvious at birth or shortly thereafter. An infant with DiGeorge syndrome may have low-set prominent ears, notched ear pinnae, a mouth without the usual bow-shaped lip, an undersized jaw, and abnormally wide-set eyes (hypertelorism) that are low-set and posteriorly angulated. Additionally, an infant may have a bifid uvula and a high, arched palate. Congenital heart anomalies are common. Cardiovascular abnormalities include great blood vessel anomalies (these may also develop soon after birth) and tetralogy of Fallot.

An infant with thymic hypoplasia (rather than aplasia) may experience a spontaneous return of cell-mediated immunity but can develop severe T-cell deficiencies later in life. This allows exaggerated susceptibility to viral, fungal, or bacterial infections, which may be overwhelming. Hypoparathyroidism, usually associated with DiGeorge syndrome, typically causes tetany, hyperphosphatemia, and hypocalcemia. Hypocalcemia (calcium levels less than 7 mg/dl) develops early and is

unusually resistant to treatment. It can lead to tetany, seizures, central nervous system damage, and early heart failure.

Rare cases of partial immunoglobulin (Ig) A deficiency have been linked to chromosome 1 and deletions of the IgA1 or IgA2 genes. Alterations in chromosome 6 suggest altered major histocompatibility complex, which is reflected in decreased T-cell responses. Aberrations in chromosome 18 are linked to facial abnormalities, nystagmus, hypotonia, atretic or stenotic ear canals, hearing loss, and mental retardation.

Diagnosis

Immediate diagnosis is difficult unless the infant has typical facial anomalies — normally the first clues to the disorder. A definitive diagnosis depends on successful treatment of hypocalcemia and other life-threatening birth defects during the first few weeks of life. Such diagnosis rests on proof of decreased or absent T lymphocytes (sheep cell test, lymphopenia), partial B-cell immunodeficiency, and of an absent thymus (chest X-ray). Immunoglobulin assays are useless because antibodies present are usually from maternal circulation.

ROLE OF THE THYMUS IN IMMUNE RESPONSE

The thymus provides an environment in which T cells develop and learn to distinguish self from nonself during fetal and early postnatal stages. Most cells that enter the thymus are destroyed. T-cell clones that react strongly to self and those that don't recognize self are deleted (negative selection). T-cell clones that recognize self but don't react strongly against self are positively selected.

After early life, mature T cells reside primarily in peripheral lymph organs and recirculate in blood and lymph.

Additional tests showing low serum calcium level, elevated serum phosphorus level, and missing parathyroid hormone confirm hypoparathyroidism.

Treatment

ALERT

Life-threatening hypocalcemia must be treated immediately, but it's unusually resistant and requires aggressive treatment, for example, with a rapid I.V. infusion of 10% solution of calcium gluconate.

During such an infusion, monitor heart rate and watch carefully to avoid infiltration. Remember that calcium supplements *must* be given with vitamin D, or sometimes also with parathyroid hormone, to ensure effective calcium utilization. After hypocalcemia is under control, a fetal thymus transplant may restore normal cell-mediated immunity. Cardiac anomalies require surgical repair when possible.

Special considerations

- Instruct the patient with DiGeorge syndrome to follow a low-phosphorus diet and educate him about measures to prevent infection.
- Teach the parents of an infant with Di-George syndrome to watch for signs of infection and have it treated immediately, to keep the infant away from crowds or any other potential sources of infection, and to provide good hygiene and adequate nutrition and hydration.
- Advise the parents to schedule and keep regular follow-up visits to the infant's pediatrician.

Acquired immunodeficiency syndrome

Acquired immunodeficiency syndrome (AIDS) is a serious secondary immunodeficiency disorder caused by the human immunodeficiency virus (HIV). Both diseases are characterized by the progressive destruction of cell-mediated (T-cell) immunity with subsequent effects on humoral (B-cell) immunity because of the pivotal role of the CD4+ helper T cells in immune reactions. Immunodeficiency makes the patient susceptible to opportunistic infections, unusual cancers, and other abnormalities. (See *Common infections and neoplasms in HIV and AIDS*.)

The Centers for Disease Control and Prevention (CDC) first described AIDS in 1981. Since then, the CDC has declared a case surveillance definition for AIDS and modified it several times, most recently in January 2000.

Causes and incidence

AIDS results from infection with HIV, which has two forms: HIV-1 and HIV-2. Both forms of HIV have the same modes of transmission and similar opportunistic infections associated with AIDS, but studies indicate that HIV-2 develops more slowly and presents with milder symptoms than HIV-1.

Transmission occurs through contact with infected blood or body fluids and is associated with identifiable high-risk behaviors. It's disproportionately represented in:

- homosexual and bisexual men
- persons who use illicit I.V. drugs
- neonates of infected females
- recipients of contaminated blood or blood products (incidence dramatically decreased since mid-1985)
- heterosexual partners of persons in the former groups.

Complications

- Opportunistic infections
- Certain cancers

Signs and symptoms

A person with HIV may remain asymptomatic for months or years. Initially, laboratory evidence or seroconversion to HIV antibodies may be the only clinical evidence of infection. However, as the disease progresses, the patient may develop generalized adenopathy and nonspecific signs and symptoms, such as weight loss, fatigue, night sweats, and fevers. As the patient's T-cell count lowers further, neurologic symptoms, opportunistic infections, and certain normally rare

cancers may develop. HIV also destroys lymph nodes and immunologic organs, leading to major dysfunctions of the immunological system. Eventually, HIV advances to AIDS. (Some individuals, termed *nonprogressors*, develop AIDS very slowly or not at all. They seem to have genetic differences that prevent the virus from attaching to certain immune receptors.)

PEDIATRIC TIP

The clinical course varies slightly in children, who have a shorter incubation time (mean, 17 months.) Signs and symptoms resemble those in adults, except for findings related to sexually transmitted disease (STD). Children show virtually all of the opportunistic infections observed in adults, with a higher incidence of bacterial infections: otitis media, pneumonias other than that caused by Pneumocystis carinii, *sepsis, chronic salivary gland enlargement, and lymphoid interstitial pneumonia.*

Diagnosis

CONFIRMING DIAGNOSIS

Signs and symptoms may occur at any time after infection with HIV, but AIDS isn't officially diagnosed until the patient's CD4+ T-cell count falls below 200 cells/mcl or the associated clinical conditions or disease.

The most commonly performed tests, antibody tests, indicate HIV infection indirectly by revealing HIV antibodies. The recommended protocol requires initial screening of individuals and blood products with an enzyme-linked immunosorbent assay (ELISA). A positive ELISA should be repeated and then confirmed by an alternate method, usually the Western blot or an immunofluorescence assay. The radioimmunoprecipitation assay is considered more sensitive and specific than the Western blot, but because it requires radioactive materials, it's a poor choice for routine screening. In addition, antibody testing isn't reliable. Because people produce detectable levels of

antibodies at different rates — a "window" varying from a few weeks to as long as 35 months in one documented case — an HIV-infected person can test negative for HIV antibodies. Antibody tests are also unreliable in neonates because transferred maternal antibodies persist for 6 to 10 months. To overcome these problems, direct tests are used, including antigen tests (p24 antigen), HIV cultures, nucleic acid probes of peripheral blood lymphocytes, and the polymerase chain reaction. (See *Laboratory tests for diagnosing and tracking HIV and assessing immune status,* page 488.)

Additional tests to support the diagnosis and help evaluate the severity of immunosuppression include CD4+ and CD8+ T-lymphocyte subset counts, erythrocyte sedimentation rate, complete blood cell count, serum $beta_2$-microglobulin, p24 antigen, neopterin levels, and anergy testing. Because many opportunistic infections in AIDS patients are reactivations of previous infections, patients are also tested for associated neoplasms, infections, and STDs.

Treatment

There is no cure for either HIV or AIDS. However, significant advances have been made to help patients control signs and symptoms and impair disease progression. Because HIV can become resistant to any drug, health care professionals use combination

treatments and multiple drug regimens to suppress the virus. Patients on medication remain infectious.

COMMON INFECTIONS AND NEOPLASMS IN HIV AND AIDS

This is a list of commonly seen disorders with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS). AIDS is diagnosed when a patient diagnosed with HIV has a CD4+ T-cell count of less than 200 cells/mcl.

- Common infections in a patient with a CD4+ count less than 350 cells/mcl include:

  - herpes simplex virus
  - herpes zoster
  - *Mycobacterium tuberculosis*
  - non-Hodgkin's lymphoma
  - oral or vaginal thrush.
- Common infections in a patient with a CD4+ count less than 200 cells/mcl include:
  - *Candida esophagitis*
  - *Pneumocystis jiroveci (carinii)* pneumonia.
- Common infections in a patient with a CD4+ count less than 100 cells/mcl include:
  - AIDS dementia
  - Cryptococcal meningitis
  - progressive multifocal leukoencephalopathy
  - toxoplasmosis encephalitis
  - wasting syndrome.
- Common infections in a patient with a CD4+ count less than 50 cells/mcl include:
  - *Cytomegalovirus* infection
  - *Mycobacterium avium.*
- Common neoplasms in patients with HIV and AIDS include:
  - Hodgkin's lymphoma
  - Kaposi's sarcoma
  - malignant lymphoma.

LABORATORY TESTS FOR DIAGNOSING AND TRACKING HIV AND ASSESSING IMMUNE STATUS

Test	Findings in HIV infection

HIV antibody tests	
▪ Enzyme-linked immunosolvent assay (ELISA)	▪ Positive test results must be confirmed by Western blot
▪ Western blot	▪ Positive
▪ Indirect immunofluorescence assay (IFA)	▪ Positive test results must be confirmed by Western blot
▪ Radioimmunoprecipitation assay (RIPA)	▪ Positive, more sensitive and specific than Western blot
▪ Home sample collection (dried blood spot, oral mucosa fluid, urine)	▪ Findings confirmed with ELISA or Western blot
HIV tracking	
▪ P24 antigen	▪ Positive for free viral protein
▪ Polymerase chain reaction (PCR)	▪ Detection of HIV ribonucleic acid (RNA) or DNA
▪ Branch deoxyribonucleic acid (bDNA)	▪ Detection of HIV RNA
▪ Nucleic acid sequence-based amplification (NASBA)	▪ Detection of HIV RNA
▪ Peripheral blood mononuclear cell (PBMC) culture for HIV-1	▪ Positive when two consecutive assays detect reverse transcriptase or p24 antigen in increasing magnitude
▪ Quantitative cell culture	▪ Measures viral load within cells
▪ Quantitative plasma culture	▪ Measures viral load by free infectious virus in the plasma
▪ β_2 microglobulin	▪ Protein is increased with disease progression
▪ Serum neopterin	▪ Increased levels seen with disease progression

Immune status	
▪ Number of CD4+ cells	▪ Decreased
▪ Percentage of CD4+ cells	▪ Decreased
▪ CD4+:CD8+ ratio	▪ Decreased
▪ White blood cell count	▪ Normal to decreased
▪ Immunoglobulin levels	▪ Increased
▪ CD4+ cell function tests	▪ CD4+ T cells have decreased ability to respond to antigen
▪ Skin test sensitivity reaction	▪ Decreased to absent

An effective method of treatment is highly active antiretroviral therapy (HAART). HAART aims to reduce the number of HIV particles in the blood as measured by viral load, thus increasing T-cell counts and improving the immunologic system's functioning. A regular and vigilant medication regimen is critical or resistance will develop because HIV strains mutate and can become resistant to HAART relatively easily.

The *nucleoside analogues* (sometimes called reverse transcriptase inhibitors) have been the mainstay of AIDS therapy in recent years. These drugs interfere with viral reverse transcriptase, which impairs HIV's ability to turn its ribonucleic acid into deoxyribonucleic acid for insertion into the host cell.

PREVENTION

PREVENTING AIDS TRANSMISSION

Health care workers and the public are advised to use precautions in all situations that risk exposure to blood, body fluids, and secretions. These precautions include:

- Educate the patient and family, sexual partners, and friends about disease transmission and prevention of

extending the disease to others.

- Inform the patient not to donate blood, blood products, organs, tissue, or sperm.
- If the patient uses I. V. drugs, caution him not to share needles.
- Inform the patient that high-risk sexual practices for AIDS transmission are those that exchange body fluids, such as vaginal or anal intercourse without a condom.
- Discuss safer sexual practices, such as hugging, petting, mutual masturbation, and protected sexual intercourse. Abstaining is also the most protective method of not transmitting the disease.
- Advise female patients of childbearing age to avoid pregnancy. Explain that an infant may become infected before birth, during delivery, or during breast-feeding.

Antiretroviral therapy typically begins when the patient's CD4+ T-cell count drops to less than 500/µl or when the patient develops an opportunistic infection. Most clinicians recommend starting the patient on a combination of these drugs in an attempt to gain the maximum benefit and to inhibit the production of resistant mutant strains of HIV. The drug combinations and dosages are then altered, depending on the patient's response.

Increasingly, physicians are basing changes in therapy on the patient's viral load rather than on his CD4+ T-cell count. Because the CD4+ count is influenced by the total white blood cell count, changes in the CD4+ count may have nothing to do with changes in the patient's HIV status. Many physicians suggest that patients on antiretroviral therapy have their viral load checked every 3 months.

The increasing use of protease inhibitors (PIs) has greatly increased the life expectancy of patients with AIDS. These drugs block the enzyme protease, which HIV needs to produce virions, the viral particles that spread the virus to other cells. The use of PIs dramatically reduces viral load — sometimes to undetectable levels — while producing a corresponding increase in the CD4+ T-cell count and, because they act at

a different site than nucleoside analogues, the PIs don't produce additional adverse effects when added to a patient's regimen.

Antiviral therapy includes the use of multiple combined drug therapies that suppress the replication of the HIV virus in the body. After antiviral therapy is initiated, treatment should be aggressive. Initially, highly active antiviral therapy, consisting of a triple drug therapy regimen — a PI and two non-nucleoside reverse transcriptase inhibitors — is recommended. In addition to these primary treatments, anti-infectives are used to combat opportunistic infections (some are used prophylactically to help patients resist opportunistic infections), and antineoplastic drugs are used to fight associated neoplasms. Supportive treatments help maintain nutritional status and relieve pain and other distressing physical and psychological symptoms.

Special considerations

- Advise health care workers and the public to use precautions in all situations that risk exposure to blood, body fluids, and secretions. Diligently practicing standard precautions can prevent the inadvertent transmission of AIDS and other infectious diseases that are transmitted by similar routes. (See *Preventing AIDS transmission*.)

- Recognize that a diagnosis of AIDS is profoundly distressing because of the disease's social impact and discouraging prognosis. The patient may lose his job and financial security as well as the support of family and friends. Do your best to help him cope with an altered body image, the emotional burden of serious illness, and the threat of death, and encourage and assist the patient in learning about AIDS societies and support programs.

Chronic mucocutaneous candidiasis

Chronic mucocutaneous candidiasis is a form of candidiasis (moniliasis) that usually develops during the first year of life but occasionally occurs as late as the 20s. Affecting males and females, it's characterized by repeated infection with *Candida albicans* that may result from an inherited defect in cell-mediated (T-cell) immunity. (Humoral [B-cell] immunity remains intact and provides a normal antibody response to *C.*

albicans.) In some patients, an autoimmune response affecting the endocrine system may induce various endocrinopathies.

Despite chronic candidiasis, these patients seldom die of systemic infection. Instead, they usually die of hepatic or endocrine failure. The prognosis for chronic mucocutaneous candidiasis depends on the severity of the associated endocrinopathy. Patients with associated endocrinopathy seldom live beyond their 30s.

Causes and incidence

No characteristic immunologic defects have been identified in this infection, but many patients have a diminished response to various antigens or to *Candida* alone. In some patients, anergy may result from deficient migration inhibition factor, a mediator normally produced by lymphocytes.

Candida species infections are the most common causes of fungal infections in patients who are immunocompromised. About 3 of every 4 females have at least one bout of vulvovaginal candidiasis during their lifetimes. In individuals who are HIVpositive, more than 90% experience oropharyngeal candidiasis and 10% have at least one episode of esophageal candidiasis.

Complications

- Addison's disease
- Nephrotoxicity
- Hypoparathyroidism
- Hypocalcemia with seizures
- Diabetes mellitus
- Pernicious anemia
- Corticotropin deficiency
- Ovarian failure

Signs and symptoms

Chronic candidal infections can affect the skin, mucous membranes, nails, and vagina, usually causing large, circular lesions. These infections seldom produce systemic symptoms but in late stages may be associated with recurrent respiratory tract infections. Other associated conditions include severe viral infections that may precede the onset of endocrinopathy and, sometimes, hepatitis. Involvement of the mouth, nose, and palate may cause speech and eating difficulties.

Symptoms of endocrinopathy are peculiar to the organ involved. Tetany and hypocalcemia are most common and are associated with hypoparathyroidism. Addison's disease, hypothyroidism, diabetes, and pernicious anemia are also connected with chronic mucocutaneous candidiasis. Psychiatric disorders are likely because of disfigurement and multiple endocrine aberrations.

Diagnosis

Laboratory findings usually show a normal circulating T-cell count, although it may be decreased. Skin tests don't usually show delayed hypersensitivity to *Candida,* even during the infectious stage. Migration inhibiting factor that indicates the presence of activated T cells may not respond to *Candida*.

Nonimmunologic abnormalities resulting from endocrinopathy may include hypocalcemia, abnormal hepatic function studies, hyperglycemia, iron deficiency, and abnormal vitamin B12 absorption (pernicious anemia). Diagnosis must rule out other immunodeficiency disorders associated with chronic *Candida* infection,

especially DiGeorge syndrome, ataxiatelangiectasia, and severe combined immunodeficiency disease, all of which produce severe immunologic defects. After diagnosis, the patient needs evaluation of adrenal, pituitary, thyroid, gonadal, pancreatic, and parathyroid function as well as careful follow-up. The disease is progressive, and most patients eventually develop endocrinopathy.

Treatment

Treatment aims to control infection but isn't always successful. Topical antifungal agents, such as clotrimazole, miconazole, and nystatin, are

useful. They may be prescribed as mouthwashes or troches (lozenges) for 5 to 10 days.

Systemic infections may not be fatal, but they're serious enough to warrant vigorous treatment. Ketoconazole and fluconazole have had some positive effect. Oral or I.M. iron replacement may also be necessary. Treatment may also include plastic surgery of the lesions, when possible, and counseling to help patients cope with their disfigurement.

Special considerations

Teach the patient about the disease's progressive manifestations and emphasize the importance of seeing an endocrinologist for regular checkups.

Chronic fatigue syndrome

Sometimes called *chronic Epstein-Barr virus,* or *myalgic encephalomyelitis,* chronic fatigue and immune dysfunction syndrome is typically marked by debilitating fatigue, neurologic abnormalities, and persistent symptoms that suggest chronic mononucleosis. It commonly occurs in adults younger than age 45, primarily in women.

Causes and incidence

The cause of chronic fatigue syndrome (CFS) is unknown, but researchers suspect that it may be found in human herpes virus-6 or in other herpesviruses, enteroviruses, or retroviruses. Recent studies have shown that inflammation of nervous system pathways, acting as an immune or autoimmune response, may play a role as well. CFS may also be associated with a reaction to viral illness that's complicated by dysfunctional immune response and by other factors that may include gender, age, genetic disposition, prior illness, stress, and environment.

Of the four million patients in the United States, less than 20% have been diagnosed.

Signs and symptoms

CFS has specific symptoms and signs, based on the exclusion of other possible causes. Its characteristic symptom is prolonged, often overwhelming fatigue that's commonly associated with a varying complex of other symptoms that are similar to those of many infections, including myalgia and cephalgia. It may develop within a few hours and can last for 6 months or more. Fatigue isn't relieved by rest and is severe enough to restrict activities of daily living by at least 50%.

Diagnosis

Because the cause and nature of CFS are still unknown, no single test unequivocally confirms its presence. Therefore, physicians base this diagnosis on the patient's history and the Centers for Disease Control (CDC) criteria. (See *Criteria for diagnosing chronic fatigue syndrome*, page 492.) Because the CDC's criteria are admittedly a working concept that may not include all forms of this disease and are based on symptoms that can result from other diseases, diagnosis is difficult and uncertain.

Treatment

No treatment is known to cure CFS. Symptomatic treatment may involve the use of medications to treat depression, anxiety, pain, discomfort, and fever. Hidden yeast infections may be present and should be treated. Antiviral drugs such as acyclovir and selected immunomodulating agents, such as I.V. gamma globulin, ampligen, and transfer factor, may be of assistance.

CRITERIA FOR DIAGNOSING CHRONIC FATIGUE SYNDROME

Because there is no blood test, brain scan, or other laboratory test to diagnose chronic fatigue syndrome (CFS), it's a diagnosis of exclusion. Following a detailed patient history, review of medications and laboratory screening tests, the physician should consider a diagnosis of CFS if two of these criteria are met:

1. Unexplained, persistent fatigue that's not due to ongoing exertion, isn't substantially relieved by rest, is of new onset (not lifelong) and results in a significant reduction in previous levels of activity.
2. Four or more of the following symptoms are present for six months or more:
   - Impaired memory or concentration
   - Postexertional malaise (extreme, prolonged exhaustion and sickness following physical or mental activity)
   - Unrefreshing sleep
   - Muscle pain
   - Multijoint pain without swelling or redness
   - Headaches or a new type or severity
   - Sore throat that's frequent or recurring
   - Tender cervical or axillary lymph nodes

From: Centers for Disease Control and Prevention, *www.cdc.gov/cfs/cfsdiagnosis.htm* 9/6/07

Special considerations

- Some patients may benefit from avoiding environmental irritants and certain foods.
- Because patients with CFS may benefit from supportive contact with others who share this disease, refer the patient to the CFS Association for information and to local support groups. Patients may also benefit from psychological counseling.

Chronic granulomatous disease

In chronic granulomatous disease (CGD), abnormal neutrophil metabolism impairs phagocytosis — one of the body's chief defense mechanisms — resulting in increased susceptibility to low-virulent or

nonpathogenic organisms, such as *Staphylococcus epidermidis*, *Escherichia coli*, *Aspergillus*, and *Nocardia*. Phagocytes attracted to sites of infection can engulf these invading organisms but are unable to destroy them. Patients with CGD may develop granulomatous inflammation, which leads to ischemic tissue damage.

Causes and incidence

CGD is inherited as a recessive X-linked trait in 50% to 60% of affected patients. Males are more likely to be affected. The genetic defect may be linked to deficiency of the enzyme NADH, NADPH oxidase, or NADH reductase. The inability of phagocytic cells to kill certain bacteria and fungi leads to long-term and repeated infections.

Signs and symptoms

Usually, the patient with CGD displays signs and symptoms associated with infections of the skin, lymph nodes, lung, liver, and bone by age 2. Skin infection is characterized by small, well-localized areas of tenderness. Seborrheic dermatitis of the scalp and axilla is also common. Lymph node infection typically causes marked lymphadenopathy with draining lymph nodes and hepatosplenomegaly. Many patients develop liver abscess, which may be recurrent and multiple; abdominal tenderness, fever, anorexia, and nausea point to abscess formation. Other common infections include osteomyelitis, which causes localized pain and fever, pneumonia, and gingivitis with severe periodontal disease.

Diagnosis

Clinical features of osteomyelitis, pneumonia, liver abscess, or chronic lymphadenopathy in a young child provide the first clues to CGD diagnosis.

CONFIRMING DIAGNOSIS

An important tool for confirming this diagnosis is the nitroblue tetrazolium (NBT) test. A clear yellow dye, NBT is normally reduced by neutrophil metabolism, resulting

in a color change from yellow to blue. Quantifying this color change estimates the degree of neutrophil metabolism.

Patients with CGD show impaired NBT reduction, indicating abnormal neutrophil metabolism. Another test measures the rate of intracellular killing by neutrophils; in CGD, killing is delayed or absent.

Other laboratory values may support the diagnosis or help monitor disease activity. Osteomyelitis typically causes elevated white blood cell count and erythrocyte sedimentation rate; bone scans help locate and size such infections. Recurrent liver or lung infection may eventually cause abnormal function studies. Cell-mediated and humoral immunity are usually normal in CGD, although some patients have hypergammaglobulinemia.

Treatment

Early, aggressive treatment of infection is the chief goal in caring for a patient with CGD. Areas of suspected infection should be biopsied or cultured, and broad-spectrum antibiotics are usually started immediately — without waiting for results of cultures. Confirmed abscesses may be drained or surgically removed. Provide meticulous wound care after such treatment, including irrigation or packing.

Many patients with CGD receive a combination of I.V. antibiotics, in many cases extended beyond the usual 10- to 14-day course. However, for fungal infections with *Aspergillus* or *Nocardia,* treatment involves amphotericin B in gradually increasing doses to achieve a maximum cumulative dose. During I.V. drug therapy, monitor vital signs frequently and rotate the I.V. site every 48 to 72 hours.

To help treat antibiotic-resistant or life-threatening infection, or to help localize infection, the patient may receive granulocyte transfusions — usually once daily until the crisis has passed. During such transfusions, watch for fever and chills (these effects can sometimes be prevented by premedication with acetaminophen). Transfusions shouldn't be given for 6 hours before or after amphotericin B to avoid severe pulmonary edema and, possibly, respiratory arrest.

Interferon-gamma may help reduce the number of severe infections. Bone marrow transplantation is also promising.

Special considerations

- If prophylactic antibiotics are ordered, teach the patient and his family how to administer them properly and how to recognize adverse effects. Advise them to promptly report any signs or symptoms of infection.
- Stress the importance of good nutrition and hygiene, especially meticulous skin and mouth care.
- During hospitalizations, encourage the patient to continue his activities of daily living as much as possible.
- If the patient is a child, arrange for a tutor to help him keep up with his schoolwork.

Severe combined immunodeficiency disease

In severe combined immunodeficiency disease (SCID), both cell-mediated (T-cell) and humoral (B-cell) immunity are deficient or absent, resulting in susceptibility to infection from all classes of microorganisms during infancy. It's the most severe form of T-cell and B-cell deficiency. At least three types of SCID exist: reticular dysgenesis, the most severe type, in which the hematopoietic stem cell fails to differentiate into lymphocytes and granulocytes; Swiss-type agammaglobulinemia, in which the hematopoietic stem cell fails to differentiate into lymphocytes alone; and enzyme deficiency, such as adenosine deaminase (ADA) deficiency, in which the buildup of toxic products in the lymphoid tissue causes damage and subsequent dysfunction.

Causes and incidence

SCID is usually transmitted as an autosomal recessive trait, although it may be X-linked. In most cases, the genetic defect seems associated with failure of the stem cell to differentiate into T and B lymphocytes. Many molecular defects such as mutation of the kinase ZAP-70 can cause SCID. X-linked SCID is due to a mutation of a subunit of the interleukin

(IL)-2, IL-4, and IL-7 receptors. Less commonly, it results from an enzyme deficiency.

SCID affects more males than females. Its estimated incidence is 1 in every 100,000 to 500,000 births. Most untreated patients die from infection within 1 year of birth.

Complications

- Infection
- Pneumonia
- Oral ulcers
- Failure to thrive
- Dermatitis

Signs and symptoms

An extreme susceptibility to infection becomes obvious in the infant with SCID in the first months of life. The infant fails to thrive and develops chronic otitis; sepsis; watery diarrhea (associated with *Salmonella* or *Escherichia coli*); recurrent pulmonary infections (usually caused by *Pseudomonas,* cytomegalovirus, or *Pneumocystis jiroveci* [formerly *carinii*]); persistent oral candidiasis, sometimes with esophageal erosions; and possibly fatal viral infections such as chickenpox.

P. jiroveci pneumonia usually strikes a severely immunodeficient infant in the first 3 to 5 weeks after birth. Onset is typically insidious, with gradually worsening cough, low-grade fever, tachypnea, and respiratory distress. Chest X-ray characteristically shows bilateral pulmonary infiltrates.

Diagnosis

Diagnosis is generally made clinically because most SCID infants suffer recurrent overwhelming infections within 1 year of birth. Some infants are diagnosed after a severe reaction to vaccination.

Defective humoral immunity is difficult to detect before age 5 months. Before then, even normal infants have very small amounts of serum immunoglobulin (Ig) M and IgA. Normal IgG levels merely reflect maternal IgG.

CONFIRMING DIAGNOSIS

Severely diminished or absent T-cell number and function, as well as lymph node biopsy showing absence of lymphocytes, can confirm diagnosis of SCID.

Treatment

Treatment aims to restore the immune response and prevent infection. Histocompatible bone marrow transplantation is the only satisfactory treatment available to correct immunodeficiency. Because bone marrow cells must be human leukocyte antigen and mixed leukocyte culture matched, the most common donors are histocompatible siblings. However, because bone marrow transplant can produce a potentially fatal graft-versus-host (GVH) reaction, newer methods of bone marrow transplant that eliminate GVH reaction (such as lectin separation and the use of monoclonal antibodies) are being evaluated.

Fetal thymus and liver transplants have achieved limited success. Immune globulin administration may also play a role in treatment. Some SCID infants have received long-term protection by being isolated in a completely sterile environment. However, this approach isn't effective if the infant already has had recurring infections.

Gene therapy is being used to treat ADA deficiency.

Special considerations

Patient care is primarily preventive and supportive.

- Constantly monitor the infant for early signs of infection. If infection develops, provide prompt and aggressive drug therapy as ordered. Watch for adverse effects of any medications given.
- Avoid vaccinations and give only irradiated blood products if a transfusion is ordered.

- Although SCID infants must remain in strict protective isolation, try to provide a stimulating atmosphere to promote growth and development. Encourage the parents to visit their child often, to hold him, and to bring him toys that can be easily sterilized.

  If the parents can't visit, call them often to report on the infant's condition. Explain all procedures, medications, and precautions to them. Maintain a normal day and night routine for the child and talk to him as much as possible.
- Because the parents will have questions about the vulnerability of future offspring, refer them for genetic counseling.
- Arrange for psychological and spiritual support for the parents and siblings to help them cope with the child's inevitable long-term illness and early death.

Complement deficiencies

Complement is a series of circulating enzymatic serum proteins with nine functional components, labeled C1 through C9. (The first four complement components are numbered out of sequence, in order of their discovery — C1, C4, C2, and C3 — but the remaining five are numbered sequentially.) When immunoglobulin (Ig) G or IgM reacts with antigens as part of an immune response, it activates C1, which then combines with C4, initiating the classic complement pathway, or cascade. (An alternative complement pathway involves the direct activation of C3 by the serum protein properdin, bypassing the initial components [C1, C4, and C2] of the classic pathway.) Complement then combines with the antigen-antibody complex and undergoes a sequence of reactions that amplify the immune response against the antigen. This complex process, which is vital to normal immune response, is called *complement fixation;* it's necessary to promote chemotaxis, opsonization, phagocytosis, bacteriolysis, and anaphylaxis reactions.

Complement deficiency or dysfunction may increase susceptibility to infection and also seems related to certain autoimmune disorders. Theoretically, any complement component may be deficient or dysfunctional, and many such disorders are under investigation. Inherited or primary complement deficiencies are rare. The most

common are C2, C4, C6, and C8 deficiencies and C5 familial dysfunction. More common secondary complement abnormalities have been confirmed in patients with lupus erythematosus, in some with dermatomyositis, in some with scleroderma, and in a few with gonococcal and meningococcal infections. The prognosis varies with the abnormality and the severity of associated diseases.

Causes and incidence

Primary complement deficiencies are inherited as autosomal recessive traits, except for deficiency of C1 esterase inhibitor, which is autosomal dominant. Secondary deficiencies may follow complement-fixing (complement-consuming) immunologic reactions, such as drug-induced serum sickness, acute streptococcal glomerulonephritis, and acute active systemic lupus erythematosus.

Inherited deficiency is rare in the general population, with an incidence of 0.03%. C2 protein deficiency disorder occurs in 1 in 10,000 persons.

Complications

- Systemic lupus erythematosus
- Glomerulonephritis
- Juvenile rheumatoid arthritis

Signs and symptoms

Clinical effects vary with the specific deficiency. C2 and C3 deficiencies and C5 familial dysfunction increase susceptibility to bacterial infection (which may involve several body systems simultaneously). C2 and C4 deficiencies are also associated with collagen vascular disease such as lupus erythematosus and with chronic renal failure. C5 dysfunction, a familial defect in infants, causes failure to thrive, diarrhea, and seborrheic dermatitis. C1 esterase inhibitor deficiency (hereditary angioedema) may cause periodic swelling in the face, hands, abdomen, or throat, with potentially fatal laryngeal edema.

Diagnosis

Diagnosis of a complement deficiency is difficult, requiring careful interpretation of both clinical features and laboratory results. Total serum complement level CH50) is low in various complement deficiencies. In addition, specific assays may be done to confirm deficiency of specific complement components. For example, detection of

complement components and IgG by immunofluorescent examination of glomerular tissues in glomerulonephritis strongly suggests complement deficiency.

Treatment

Primary complement deficiencies have no known cure. Associated infection, collagen vascular disease, or renal disease requires prompt, appropriate treatment. Transfusion of fresh frozen plasma to provide replacement of complement components is controversial because replacement therapy doesn't cure complement deficiencies, and any beneficial effects are transient. A bone marrow transplant may be helpful but can cause a potentially fatal graft-versus-host reaction (GVHR). Anabolic steroids such as danazol and antifibrinolytic agents are often used to reduce acute swelling in patients with C1 esterase inhibitor deficiency.

Special considerations

- Teach the patient (or his family, if he's a child) the importance of avoiding infection, how to recognize its early signs and symptoms, and the need for prompt treatment if it occurs.
- After a bone marrow transplant, monitor the patient closely for signs of a transfusion reaction or GVHR.
- Meticulous patient care can speed recovery and prevent complications. For example, a patient with renal infection needs careful monitoring of intake and output, tests for serum electrolytes and acid-base balance, and observation for signs of renal failure.
- When caring for a patient with hereditary angioedema, be prepared for emergency management of laryngeal edema; keep airway