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Hematologic disorders

Introduction

Blood, one of the body's major fluid tissues, continuously circulates through the heart and blood vessels, carrying vital elements to every part of the body.

Blood basics

Blood performs several vital functions through its special components: the liquid portion (plasma) and the formed constituents (erythrocytes, leukocytes, and thrombocytes) that are suspended in it. Erythrocytes (red blood cells [RBCs]) carry oxygen to the tissues and remove carbon dioxide from them. Leukocytes (white blood cells [WBCs]) act in inflammatory and immune responses. Plasma (a clear, straw-colored fluid) carries antibodies and nutrients to tissues and carries waste away; plasma coagulation factors and thrombocytes (platelets) control clotting. (See *Coagulation factors,* page 498.)

Typically, the average person has 5 to 6 L of circulating blood, which constitute 5% to 7% of body weight (as much as 10% in premature neonates). Blood is three to five times more viscous than water, with an alkaline pH of 7.35 to 7.45, and is either bright red (arterial blood) or dark red (venous blood), depending on the degree of oxygen saturation and the hemoglobin (Hb) level.

COAGULATION FACTORS

Factor	Synonym	Location

Factor I	Fibrinogen	Plasma
Factor II	Prothrombin	Plasma
Factor III	Tissue thromboplastin	Tissue cells
Factor IV	Calcium ion	Plasma
Factor V	Labile factor	Plasma
Factor VII	Stable factor	Plasma
Factor VIII	Antihemophilic globulin or antihemophilic factor A	Plasma
Factor IX	Plasma thromboplastin component, Christmas factor	Plasma
Factor X	Stuart-Prower factor	Plasma
Factor XI	Plasma thromboplastin antecedent	Plasma
Factor XII	Hageman factor	Plasma
Factor XIII	Fibrin stabilizing factor	Plasma

Formation and characteristics

Hematopoiesis, the process of blood formation, occurs primarily in the bone marrow of the femur, sternum, and vertebrae, where primitive blood cells (stem cells) produce the precursors of erythrocytes (normoblasts), leukocytes, and thrombocytes. During embryonic development, blood cells are derived from mesenchyma and form in the yolk sac. As the fetus matures, blood cells are produced in the liver, the spleen, and the thymus; by the fifth month of gestation, blood cells also begin to form in bone marrow. After birth, blood cells are usually produced only in the marrow.

Blood's function

The most important function of blood is to *transport oxygen* (bound to RBCs inside Hb) from the lungs to the body tissues and to *return carbon dioxide* from these tissues to the lungs. Blood also performs the following functions:

- production and delivery of antibodies (by WBCs) formed by plasma cells and lymphocytes
- transportation of granulocytes and monocytes to defend the body against pathogens by phagocytosis
- immunity against viruses and cancer cells through sensitized lymphocytes
- provision of complement, a group of immunologically important protein substances in plasma essential for immune and inflammatory responses.

Blood's other functions include control of hemostasis by platelets, plasma, and coagulation factors that repair tissue injuries and prevent or halt bleeding; acid-base and fluid balance; regulation of body temperature by carrying off excess heat generated by the internal organs for dissipation through the skin; and transportation of nutrients and regulatory hormones to body tissues and of metabolic wastes to the organs of excretion (kidneys, lungs, and skin).

Blood dysfunction

Because of the rapid reproduction of bone marrow cells and the short life span and minimal storage in the bone marrow of circulating cells, bone marrow cells and their precursors are particularly vulnerable to physiologic changes that can affect cell production. Resulting blood disorders may be primary or secondary, quantitative or qualitative, or both; they may involve some or all blood components. Quantitative blood disorders result from increased or decreased cell production or cell destruction; qualitative blood disorders stem from intrinsic cell abnormalities or plasma component dysfunction. Specific causes of blood disorders include trauma, chronic disease, surgery, malnutrition, drugs, exposure to toxins and radiation, and genetic and congenital defects that disrupt production and function. For example, depressed

bone marrow production or mechanical destruction of mature blood cells can reduce the number of RBCs, platelets, and granulocytes, resulting in pancytopenia (anemia, thrombocytopenia, and granulocytopenia). Increased production of multiple bone marrow components can follow myeloproliferative disorders.

Erythropoiesis

The tissues' demand for oxygen and the blood cells' ability to deliver it regulate RBC production. Consequently, hypoxia (or tissue anoxia) stimulates RBC production by triggering the formation and release of erythropoietin, a hormone (probably produced by the kidneys) that activates bone marrow to produce RBCs. Erythropoiesis may also be stimulated by androgens (which accounts for higher RBC counts in men). RBCs have a life span of approximately 120 days.

The actual formation of an erythrocyte begins with an uncommitted stem cell that may eventually develop into an RBC or a WBC. Such formation requires certain vitamins—B_{12} and folic acid—and minerals, such as copper, cobalt, and especially iron, which is vital to hemoglobin's oxygen-carrying capacity. Iron is obtained from various foods and is absorbed in the duodenum and upper jejunum, leaving the excess for temporary storage in reticuloendothelial cells, especially those in the liver. Iron excess is stored as ferritin and hemosiderin until it's released for use in the bone marrow to form new RBCs.

ELDER TIP

In older adults, fatty bone marrow replaces some active cell-forming marrow—first in the long bones and later in the flat bones. The altered bone marrow can't increase erythrocyte production as readily as before in response to such stimuli as hormones, anoxia, hemorrhage, and hemolysis.

RBC disorders

RBC disorders include quantitative and qualitative abnormalities. Deficiency of RBCs (anemia) can follow any condition that destroys or

inhibits the formation of these cells. Common factors leading to this deficiency include:

- chronic illnesses, such as renal disease, cancer, and chronic infections
- congenital or acquired defects that cause bone marrow aplasia and suppress general hematopoiesis (aplastic anemia) or erythropoiesis
- deficiencies of vitamins (vitamin B12 deficiency or pernicious anemia) or minerals (iron, folic acid, copper, and cobalt deficiency anemias) that cause inadequate RBC production
- drugs, toxins, and ionizing radiation
- excessive chronic or acute blood loss (posthemorrhagic anemia)
- intrinsically or extrinsically defective red cells (sickle cell anemia and hemolytic transfusion reaction)
- metabolic abnormalities (sideroblastic anemia).

Comparatively few conditions lead to excessive numbers of RBCs:

- abnormal proliferation of all bone marrow elements (polycythemia vera), especially RBC mass
- a single-element abnormality (for instance, an increase in RBCs that results from erythropoietin excess, which in turn results from hypoxemia, hypertension, or pulmonary disease)
- decreased plasma cell volume, which produces a corresponding relative increase in RBC concentration (such as through the use of drugs).

Function of WBCs

WBCs, or leukocytes, protect the body against harmful bacteria and infection and are classified as granular leukocytes (basophils, neutrophils, and eosinophils) or nongranular leukocytes (lymphocytes, monocytes, and plasma cells). (See *Two types of leukocytes*.) Usually, WBCs are produced in bone marrow; lymphocytes and plasma cells are produced in lymphoid tissue as well. Neutrophils have a circulating half-

life of less than 6 hours; some lymphocytes may survive for weeks or months. Normally, WBCs number between 5,000 and 10,000/µl.

There are six types of WBCs:

- *Neutrophils,* the predominant form of granulocyte, make up about 60% of WBCs; they help devour invading organisms by phagocytosis.
- *Eosinophils,* minor granulocytes, may defend against parasites and lung and skin infections and act in allergic reactions. They account for 1% to 5% of the total WBC count.
- *Basophils,* minor granulocytes, may release heparin and histamine into the blood and participate in delayed hypersensitivity reactions. They account for 0% to 1% of the total WBC count.
- *Monocytes,* along with neutrophils, help devour invading organisms by phagocytosis. They help process antigens for lymphocytes and form macrophages in the tissues; they account for 1% to 6% of the total WBC count.
- *Lymphocytes* occur as B cells and T cells. B cells aid antibody synthesis; T cells regulate cell-mediated immunity. They account for 20% to 40% of the total WBC count.
- *Plasma cells* develop from lymphocytes, reside in the tissue, and produce antibodies.

A temporary increase in production and release of mature WBCs (leukemic reaction) is a normal response to infection. However, an excessive number of immature WBC precursors and their accumulation in bone marrow or lymphoid tissue is characteristic of leukemia. These nonfunc-tioning WBCs (blasts) provide no protection against infection; crowd out RBCs, platelets, and mature WBCs; and spill into the bloodstream, sometimes infiltrating organs and impairing function.

WBC deficiencies may reflect inadequate cell production, drug reactions, ionizing radiation, infiltrated bone marrow (cancer), congenital defects, aplastic anemia, folic acid deficiency, or hypersplenism. The major WBC deficiencies are granulocytopenia, lymphocytopenia, and monocytopenia.

Platelets, plasma, and clotting

Platelets are small (2 to 4 microns in diameter), colorless, disk-shaped cytoplasmic fragments split from cells in bone marrow called megakaryocytes. The normal platelet concentration is 150,000 to 400,000/µl. These fragments, which have a life span of approximately 10 days, perform three vital functions:

- initiate vasoconstriction of damaged blood vessels to minimize blood loss
- form hemostatic plugs in injured blood vessels
- with plasma, provide materials that accelerate blood coagulation—notably platelet factor 3.

Plasma consists mainly of proteins (chiefly albumin, globulin, and fibrinogen) held in aqueous suspension. Other components of plasma include glucose, lipids, amino acids, electrolytes, pigments, hormones, respiratory gases (oxygen and carbon dioxide), and products of metabolism, such as urea, uric acid, creatinine, and lactic acid. Its fluid characteristics— including osmotic pressure, viscosity, and suspension qualities—depend on its protein content. Plasma components regulate acid-base balance and immune responses and mediate coagulation and nutrition.

In a complex process called *hemostasis,* platelets, plasma, and coagulation factors interact to control bleeding.

Hemostasis and the clotting mechanism

Hemostasis is the complex process by which the body controls bleeding. When a blood vessel ruptures, local vasoconstriction and platelet clumping (aggregation) at the injury site initially help prevent hemorrhage. This activation of the coagulation system, called *extrinsic cascade,* requires release

of tissue thromboplastin from the damaged cells. However, formation of a more stable clot requires initiation of the complex clotting mechanism known as the *intrinsic cascade system*. When endothelial vessel injury or a foreign body in the bloodstream activates this system, *activating factor XII* triggers clotting. In the final common pathway, prothrombin is

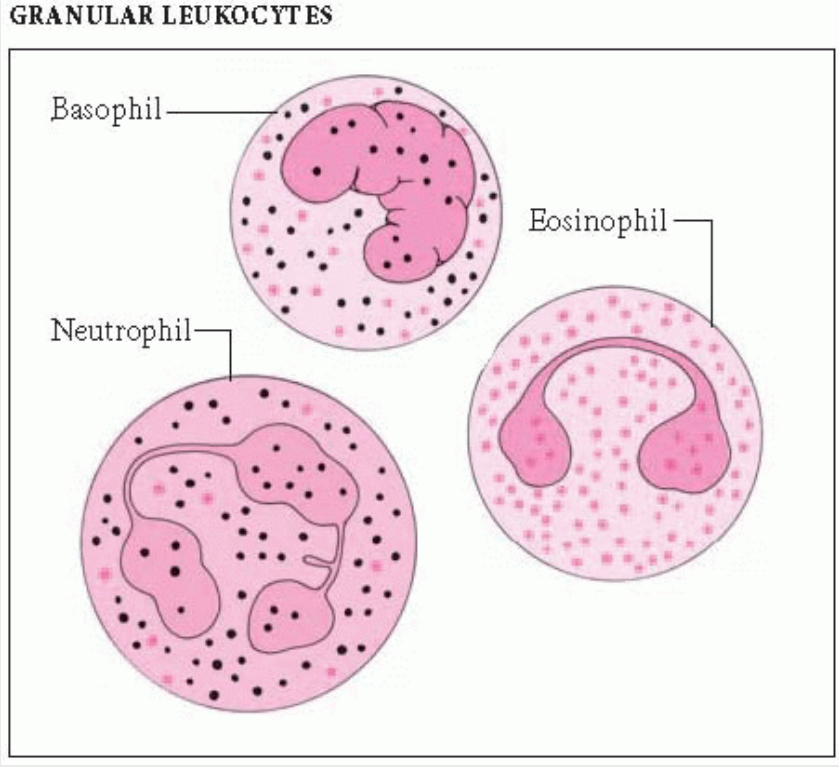
converted to thrombin and fibrinogen to fibrin, which is necessary for creation of a fibrin clot.

TWO TYPES OF LEUKOCYTES

Leukocytes vary in size, shape, and number.

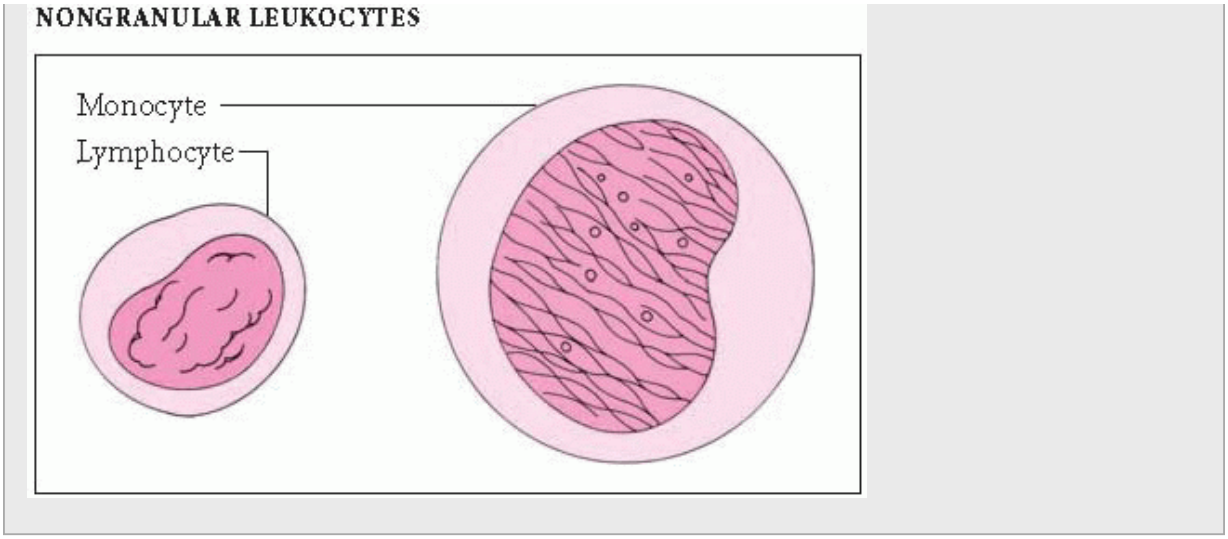
Granular leukocytes

Granular leukocytes (granulocytes) are the most numerous and include basophils, containing cytoplasmic granules that stain readily with alkaline dyes; eosinophils, which stain with acidic dyes; and neutrophils, which are finely granular and recognizable by their multinucleated appearance.



Nongranular leukocytes

Lymphocytes and monocytes have few, if any, granulated particles in the cytoplasm.



Therapy with blood components

Because of improved methods of collection, component separation, and storage, blood transfusions are being used more effectively than ever. Separating blood into components permits a single unit of blood to benefit several patients with different hematologic abnormalities. Component therapy allows replacement of a specific blood component without risking reactions from other components.

Blood typing, crossmatching, and human leukocyte antigen (HLA) typing are compatibility tests used to ensure safe, effective

replacement therapy and minimize the risk of transfusion reactions. Blood typing determines the antigens present in the patient's RBCs by reaction with standardized sera. (Critical antigen groups are those of ABO and Rh factor.) Crossmatching the patient's blood with transfusion blood provides some assurance that the patient doesn't have antibodies against donor red cells. HLA typing may be helpful for the patient who needs long-term transfusion therapy or frequent platelet transfusions, but usually, only family members can provide an appropriate match because antigenic properties are genetically determined.

Bone marrow transplantation

Bone marrow transplantation is used to treat acute leukemia, aplastic anemia, severe combined immunodeficiency disease, Nezelof syndrome, and Wiskott-Aldrich syndrome. In this procedure, marrow from a twin or

another HLA-identical donor (usually a sibling) is transfused in an attempt to repopulate the recipient's bone marrow with normal cells.

A hematologic disorder can affect nearly every aspect of the patient's life, perhaps resulting in life-threatening emergencies that require prompt medical treatment. Astute, sensitive care founded on a firm understanding of hematologic basics can help the patient survive such illnesses. In situations with poor prognoses, the patient may need to make many adjustments to maintain an optimal quality of life.

ANEMIAS

Pernicious anemia

Pernicious anemia, also known as *Addison's anemia,* is a megaloblastic anemia characterized by decreased gastric production of hydrochloric acid and deficiency of intrinsic factor (IF), a substance normally secreted by the parietal cells of the gastric mucosa that's essential for vitamin B_{12} absorption in the ileum. The resulting deficiency of vitamin B_{12} causes serious neurologic, gastric, and intestinal abnormalities. Untreated pernicious anemia may lead to permanent neurologic disability and death.

Causes and incidence

Familial incidence of pernicious anemia suggests a genetic predisposition. (It may involve an inherited single dominant autosomal factor.) Significantly higher incidence in patients with immunologically related diseases, such as thyroiditis, myxedema, and Graves' disease, seems to support a widely held theory that an inherited autoimmune response causes gastric mucosal atrophy and, therefore, deficiency of hydrochloric acid and IF. IF deficiency impairs vitamin B_{12} absorption. The resultant vitamin B_{12} deficiency inhibits cell growth, particularly of red blood cells (RBCs), leading to insufficient and deformed RBCs with poor oxygen-carrying capacity. It also impairs myelin formation, causing neurologic damage. Iatrogenic induction can follow partial gastrectomy.

PEDIATRIC TIP

Juvenile pernicious anemia, occurring in children younger than age 10, stems from a congenital stomach disorder that causes secretion of abnormal IF.

ELDER TIP

With age, vitamin B_{12} absorption may also diminish, resulting in reduced erythrocyte mass and decreased hemoglobin (Hb) levels and hematocrit (HCT).

Pernicious anemia primarily affects people of northern European ancestry. It's rare in children and infants. Onset typically occurs after age 35, and incidence increases with age. It affects about 2% of people older than age 60.

Complications

- Paralysis
- Psychotic behavior
- Sphinctor control loss of bowel and bladder

Signs and symptoms

Characteristically, pernicious anemia has an insidious onset but eventually causes an unmistakable triad of symptoms: weakness, sore tongue, and numbness and tingling in the extremities. The lips, gums, and tongue appear markedly bloodless. Hemolysis-induced hyperbilirubinemia

may cause faintly jaundiced sclera and pale to bright yellow skin. In addition, the patient may become highly susceptible to infection, especially of the genitourinary tract.

Other systemic symptoms of pernicious anemia include the following:

- *GI*—Gastric mucosal atrophy and decreased hydrochloric acid production disturb digestion and lead to nausea, vomiting, anorexia, weight loss, flatulence, diarrhea, and constipation. Gingival bleeding and tongue inflammation may hinder eating and intensify anorexia.

- *Central nervous system (CNS)*—Demyelination caused by vitamin B_{12} deficiency initially affects the peripheral nerves but gradually extends to the spinal cord. Consequently, the neurologic effects of pernicious anemia may include neuritis; weakness in extremities; peripheral numbness and paresthesia; disturbed position sense; lack of coordination; ataxia; impaired fine finger movement; positive Babinski's and Romberg's signs; lightheadedness; altered vision (diplopia and blurred vision), taste, and hearing (tinnitus); optic muscle atrophy; loss of bowel and bladder control; and, in males, impotence. Its effects on the nervous system may also produce irritability, poor memory, headache, depression, and delirium. Although some of these symptoms are temporary, irreversible CNS changes may have occurred before treatment.
- *Cardiovascular*—Increasingly fragile cell membranes induce widespread destruction of RBCs, resulting in low Hb levels. The impaired oxygen-carrying capacity of the blood secondary to lowered Hb leads to weakness, fatigue, and light-headedness. Compensatory increased cardiac output results in palpitations, wide pulse pressure, dyspnea, orthopnea, tachycardia, premature beats and, eventually, heart failure.
- *Musculoskeletal*—Scissors gait can also occur as a late sign of untreated anemia.

Diagnosis

A positive family history, typical ethnic heritage, and results of blood studies, bone marrow aspiration, gastric analysis, and the Schilling test establish the diagnosis. (See *Tests for blood composition, production, and function,* pages 504 and 505.) Laboratory screening must rule out other anemias with similar symptoms, such as folic acid deficiency anemia, because treatment differs. Diagnosis must also rule out vitamin B_{12} deficiency resulting from malabsorption due to GI disorders, gastric surgery, radiation, or drug therapy.

Blood study results that suggest pernicious anemia include:

- decreased Hb levels (4 to 5 g/dl) and decreased RBC count

ELDER TIP

Hb levels drop 1 to 2 g/dl in elderly men, and HCT may decrease slightly in both men and women. These changes reflect decreased bone marrow and hematopoiesis and (in men) decreased androgen levels; they aren't an indicator of pernicious anemia.

- increased mean corpuscular volume (greater than 120/µl); because larger-than-normal RBCs *each* contain increased amounts of Hb, mean corpuscular Hb concentration is also increased
- possible low white blood cell and platelet counts and large, malformed platelets
- serum vitamin B_{12} assay levels less than 0.1 mcg/ml
- elevated serum lactate dehydrogenase levels.

Bone marrow aspiration reveals erythroid hyperplasia (crowded red bone marrow), with increased numbers of megaloblasts but few normally developing RBCs. Gastric analysis shows absence of free hydrochloric acid after histamine or pentagastrin injection.

CONFIRMING DIAGNOSIS

The Schilling test is the definitive test for pernicious anemia. In this test, the patient receives a small oral dose (0.5 to 2 mcg) of radioactive vitamin B_{12} after fasting for 12 hours. A larger dose (1 mg) of nonradioactive vitamin B_{12} is given I.M. 2 hours later, as a parenteral flush, and the radioactivity of a 24-hour urine specimen is measured. About 7% of the radioactive B_{12} dose is excreted in the first 24 hours; people with pernicious anemia excrete less than 3%. (In pernicious anemia, the vitamin remains unabsorbed and is passed in the stool.) When the Schilling test is repeated with IF added, the test shows normal excretion of vitamin B_{12}.

TESTS FOR BLOOD COMPOSITION, PRODUCTION, AND FUNCTION

Overall composition

- Peripheral blood smear shows maturity and morphologic characteristics of blood elements and determines qualitative abnormalities.
- Complete blood count determines the actual number of blood elements in relation to volume and quantifies abnormalities.
- Bone marrow aspiration or biopsy allows evaluation of hematopoiesis by showing blood elements and precursors, and abnormal or malignant cells.

Red blood cell function

- Hematocrit, or packed cell volume, measures the percentage of red blood cells (RBCs) per fluid volume of whole blood.
- Hemoglobin (Hb) measures the amount (grams) of Hb per deciliter of blood, to determine oxygen-carrying capacity.
- Reticulocyte count assesses RBC production by determining concentration of this erythrocyte precursor.
- Schilling test determines absorption of vitamin B_{12} (necessary for erythropoiesis) by measuring excretion of radioactive B_{12} in the urine.
- Mean corpuscular volume describes the RBC in terms of size.
- Mean corpuscular Hb determines the average amount of Hb per RBC.
- Mean corpuscular Hb concentration establishes the average Hb concentration in 1 dl of packed RBCs.

- Sucrose hemolysis test assesses the susceptibility of RBCs to hemolyze with complement.
- Direct Coombs' test demonstrates the presence of immunoglobulin G (IgG) antibodies (such as antibodies to Rh factor) or, possibly, complement on circulating RBCs.
- Indirect Coombs' test, a two-step test, detects the presence of IgG antibodies in the serum.
- Sideroblast test detects stainable iron (available for Hb synthesis) in normoblastic RBCs.
- Hb electrophoresis demonstrates abnormal Hb such as sickle cell.

Hemostasis

- Platelet count determines the number of platelets.
- Bleeding time (Ivy bleeding time) assesses the capacity for platelets to stop bleeding in capillaries and small vessels.
- Prothrombin time (Quick's test, pro time) assists in evaluation of thrombin generation (extrinsic clotting mechanism).
- Partial thromboplastin time aids evaluation of the adequacy of plasma-clotting factors (intrinsic clotting mechanism).
- International Normalized Ratio (INR) normalizes ratios between labs.
- Fibrin degradation products (fibrin split products, FDPs) test the amount of clot breakdown products in serum.
- Thrombin time detects abnormalities in thrombin fibrinogen reaction.
- Fibrinogen (factor I) measures this coagulation factor in plasma.

- D-dimer test determines if FDPs are from normal mechanisms or excessive fibrinolysis and is commonly used to diagnose disseminated intravascular coagulation.

White blood cell function

- White blood cell (WBC) count, differential establishes quantity and maturity of WBC elements (neutrophils [called polymorphonuclear granulocytes or bands], basophils, eosinophils, lymphocytes, monocytes).
- Quantified $CD4^+$:$CD8^+$ T lymphocytes determines helper:suppressor ratio important to immune function with human immunodeficiency virus infection.

Plasma

- Erythrocyte sedimentation rate measures the rate of RBCs settling from plasma and may reflect infection.
- Electrophoresis of serum proteins determines the amount of various serum proteins (classified by mobility in response to an electrical field). It's commonly used to diagnose plasma cell myeloma.
- Immunoelectrophoresis of serum proteins separates and classifies serum antibodies (immunoglobulins) through specific antisera.

Important serologic findings may include IF antibodies and antiparietal cell antibodies.

Treatment

Early parenteral vitamin B_{12} replacement can reverse pernicious anemia, minimize complications and, possibly, prevent permanent neurologic damage. An initial high dose of parenteral vitamin B_{12} causes rapid RBC regeneration. Within 2 weeks, Hb levels should rise to normal, and the patient's condition should markedly improve. Because rapid cell regeneration increases the patient's iron and folate requirements,

concomitant iron and folic acid replacement is necessary to prevent iron deficiency anemia.

After the patient's condition improves, the vitamin B_{12} dosage can be decreased to maintenance levels and given monthly. Because such injections must be continued for life, the patient should learn self-administration of vitamin B_{12}.

If anemia causes extreme fatigue, the patient may require bed rest until Hb levels rise. If Hb levels are dangerously low, he may need blood transfusions. Digoxin (Lanoxin), a diuretic, and a low-sodium diet may be necessary for a patient with heart failure. Most important is the replacement of vitamin B_{12} to control the condition that led to this failure. Antibiotics help combat accompanying infections.

Special considerations

Supportive measures minimize the risk of complications and speed recovery. Patient and family teaching can promote compliance with lifelong vitamin B_{12} replacement.

- If the patient has severe anemia, plan activities, rest periods, and necessary diagnostic tests to conserve his energy. Monitor pulse rate often; tachycardia means his activities are too strenuous.
- To ensure accurate Schilling test results, make sure that all urine over a 24-hour period is collected and that the specimens are uncontaminated.
- Warn the patient to guard against infections and tell him to report signs of infection promptly, especially pulmonary and urinary tract infections, because the patient's weakened condition may increase susceptibility.
- Provide a well-balanced diet, including foods high in vitamin B_{12} (meat, liver, fish, eggs, and milk). Offer between-meal snacks and encourage the family to bring favorite foods from home.
- Because a sore mouth and tongue make eating painful, ask the dietitian to avoid giving the patient irritating foods. If these symptoms make talking difficult, supply a pad and pencil or some other aid to

facilitate nonverbal communication; explain this problem to the family. Provide diluted mouthwash or, with severe conditions, swab the patient's mouth with tap water or warm saline solution or use topical anesthetic mouthwash.

- Warn the patient with a sensory deficit not to use a heating pad, because it may cause burns.
- If the patient is incontinent, establish a regular bowel and bladder routine. After the patient is discharged, a home health care nurse should follow up on this schedule and make adjustments, as needed.
- If neurologic damage causes behavioral problems, assess mental and neurologic status often; if needed, give tranquilizers, as ordered, and apply wrist or jacket restraint and utilize bed alert alarm at night.
- Stress that vitamin B_{12} replacement isn't a permanent cure and that these injections *must* be continued for life, even after symptoms subside.

PREVENTING FOLIC ACID DEFICIENCY ANEMIA

Folic acid (pteroylglutamic acid, folacin) is found in most body tissues, where it acts as a coenzyme in metabolic processes involving one carbon transfer. It's essential for formation and maturation of red blood cells and for synthesis of deoxyribonucleic acid. Although its body stores are relatively small (about 70 mg), this vitamin is plentiful in most well-balanced diets.

However, because folic acid is water-soluble and heat-labile, it's easily destroyed by cooking. Also, approximately 20% of folic acid intake is excreted unabsorbed. Insufficient daily folic acid intake (less than 50 mcg/ day) usually induces folic acid deficiency within 4 months. To prevent folic acid deficiency anemia, foods high in folic acid content should be chosen, such as those listed below:

Food	mcg/100 g

Asparagus spears	109
Beef liver	294
Broccoli spears	54
Collards (cooked)	102
Mushrooms	24
Oatmeal	33
Peanut butter	57
Red beans	180
Wheat germ	305

PREVENTION

To prevent pernicious anemia, emphasize the importance of vitamin B_{12} supplements for patients who have had extensive gastric resections or who follow strict vegetarian or vegan diets.

Folic acid deficiency anemia

Folic acid deficiency anemia is a common, slowly progressive, megaloblastic anemia. It usually occurs in infants, adolescents, pregnant and lactating females, alcoholics, elderly people, and people with malignant or intestinal diseases.

Causes and incidence

Folic acid deficiency anemia may result from:

- alcohol abuse (alcohol may suppress metabolic effects of folate)
- poor diet (common in alcoholics, elderly people living alone, and infants, especially those with infections or diarrhea)

- impaired absorption (due to intestinal dysfunction from disorders such as celiac disease, tropical sprue, regional jejunitis, or bowel resection)
- bacteria competing for available folic acid
- excessive cooking, which can destroy a high percentage of folic acids in foods (See *Preventing folic acid deficiency anemia*.)
- limited storage capacity in infants
- prolonged drug therapy (anticonvulsants and estrogens)
- increased folic acid requirements during pregnancy; during rapid growth in infancy (common because of recent increase in survival of premature infants); during childhood and adolescence (because of general use of folate-poor cow's milk); and in patients with neoplastic diseases and some skin diseases (chronic exfoliative dermatitis).

It's estimated that 10% of the United States population has low folate stores.

Signs and symptoms

Folic acid deficiency anemia gradually produces clinical features characteristic of other megaloblastic anemias, without the neurologic manifestations: progressive fatigue, shortness of breath, palpitations, weakness, glossitis, nausea, anorexia, headache, fainting, irritability, forgetfulness, pallor, and

slight jaundice. Folic acid deficiency anemia doesn't cause neurologic impairment unless it's associated with vitamin B_{12} deficiency, as in pernicious anemia.

Diagnosis

CONFIRMING DIAGNOSIS

The Schilling test and a therapeutic trial of vitamin B_{12} injections distinguish between folic acid deficiency anemia and pernicious anemia. Significant findings

include macrocytosis, decreased reticulocyte count, abnormal platelets, and serum folate less than 3 ng/ml.

Treatment

Treatment consists primarily of folic acid supplements and elimination of contributing causes. Folic acid supplements may be given orally or parenterally (to patients who are severely ill, have malabsorption, or are unable to take oral medication). Many patients respond favorably to a well-balanced diet. If the patient has combined B_{12} and folate deficiencies, folic acid replenishment alone may aggravate neurologic dysfunction.

Special considerations

- Teach the patient to meet daily folic acid requirements by including a food from each food group in every meal. If he has a severe deficiency, explain that diet only reinforces folic acid supplementation and isn't therapeutic by itself. Urge compliance with the prescribed course of therapy. Advise him not to stop taking the supplements when he begins to feel better.
- If the patient has glossitis, emphasize the importance of good oral hygiene. Suggest regular use of mild or diluted mouthwash and a soft toothbrush.
- Watch fluid and electrolyte balance, particularly in the patient who has severe diarrhea and is receiving parenteral fluid replacement therapy.
- Because anemia causes severe fatigue, schedule regular rest periods until the patient is able to resume normal activity.

PREVENTION

Emphasize the importance of a well-balanced diet high in folic acid. Identify alcoholics with poor dietary habits and try to arrange for appropriate counseling. Tell mothers who aren't breast-feeding to use commercially prepared formulas.

Aplastic anemias

Aplastic, or hypoplastic, anemias result from injury to or destruction of stem cells in bone marrow or the bone marrow matrix, causing pancytopenia (anemia, granulocytopenia, and thrombocytopenia) and bone marrow hypoplasia. Although commonly used interchangeably with other terms for bone marrow failure, aplastic anemias properly refer to pancytopenia resulting from the decreased functional capacity of a hypoplastic, fatty bone marrow. These disorders generally produce fatal bleeding or infection, particularly when they're idiopathic or stem from chloramphenicol or from infectious hepatitis. Mortality for aplastic anemias with severe pancytopenia is 80% to 90%.

Causes and incidence

Aplastic anemias usually develop when damaged or destroyed stem cells inhibit red blood cell (RBC) production. Less commonly, they develop when damaged bone marrow microvasculature creates an unfavorable environment for cell growth and maturation. About one-half of such anemias result from drugs (antibiotics, anticonvulsants, anti-inflammatory drugs, an-tineoplastics, diuretics, phenothiazines, antidiabetics, and antithyroid drugs), toxic agents (such as benzene and chloramphenicol), or radiation. The rest may result from immunologic factors (unconfirmed), severe disease (especially hepatitis), viral infection (especially in children), or preleukemic and neoplastic infiltration of bone marrow.

Idiopathic anemias may be congenital. Two such forms of aplastic anemia have been identified: Congenital hypoplastic anemia (Blackfan-Diamond anemia) develops between ages 2 and 3 months; Fanconi's syndrome, between birth and age 10. In Fanconi's syndrome, chromosomal abnormalities are usually associated with multiple congenital anomalies, such as dwarfism, and hypoplasia of the kidneys and spleen. In the absence of a consistent

familial or genetic history of aplastic anemia, researchers suspect that these congenital abnormalities result from an induced change in the fetus' development.

BONE MARROW TRANSPLANTATION

In bone marrow transplantation, usually 500 to 700 ml of marrow is aspirated from the pelvic bones of a human leukocyte antigen (HLA)-compatible donor (allogeneic) or of the recipient himself during complete remission (autologous). The aspirated marrow is filtered and then infused into the recipient in an attempt to repopulate the patient's marrow with normal cells. This procedure has effected long-term, healthy survival in about 50% of patients with severe aplastic anemia. Bone marrow transplantation may also be effective in patients with acute leukemia, certain immunodeficiency diseases, and solid tumor neoplasms.

Because bone marrow transplantation carries serious risks, it requires strict adherence to infection control and strict sterile techniques, and a primary nurse to provide consistent care and continuous monitoring of the patient's status.

Before transplantation

- Explain that the success rate depends on the stage of the disease and an HLA-identical match.
- After bone marrow aspiration is completed under local anesthetic, apply pressure dressings to the donor's aspiration sites. Observe the sites for bleeding. Relieve pain with analgesics and ice packs, as needed.
- Assess the patient's understanding of bone marrow transplantation. If necessary, correct any misconceptions about this procedure and provide additional information, as appropriate. Prepare the patient to expect an extended hospital stay. Explain that chemotherapy and possible radiation treatments are necessary to destroy cells that may cause the body to reject the transplant.

- Various treatment protocols are used. For example, I.V. cyclophosphamide may be used with additional chemotherapeutic agents or total body irradiation and requires aggressive hydration to prevent hemorrhagic cystitis. Control nausea and vomiting with an antiemetic, such as ondansetron, prochlorperazine, metoclopramide, or lorazepam, as needed. Give allopurinol, as prescribed, to prevent hyperuricemia resulting from tumor breakdown products. Because alopecia is a common adverse effect of high-dose cyclophosphamide therapy, encourage the patient to choose a wig or scarf before treatment begins.
- Total body irradiation may follow chemotherapy, inducing total marrow aplasia. Warn the patient that cataracts, GI disturbances, and sterility are possible adverse effects.
- Assess venous access. If necessary, the patient may have an indwelling central venous catheter inserted.

During marrow infusion

- Monitor vital signs every 15 minutes.
- Watch for complications of marrow infusion, such as pulmonary embolus, hypersensitivity reactions, and volume overload.
- Reassure the patient throughout the procedure.

After the infusion

- Continue to monitor the patient's vital signs every 15 minutes for 2 hours after infusion, then every 4 hours. Watch for fever and chills, which may be the only signs of infection. Give prophylactic antibiotics as prescribed. To reduce the possibility of bleeding, don't administer medications rectally or I.M.

- Administer methotrexate or cyclosporine, as prescribed, to prevent graft-versus-host (GVH) reaction, a potentially fatal complication of allogeneic transplantation. Watch for signs or symptoms of GVH reaction, such as maculopapular rash, pancytopenia, jaundice, joint pain, and generalized edema.
- Administer vitamins, steroids, and iron and folic acid supplements, as appropriate. Administration of blood products, such as platelets and packed red blood cells, may also be indicated, depending on the results of daily blood studies.
- Provide good mouth care every 2 hours. Use hydrogen peroxide and nystatin mouthwash or oral fluconazole, for example, to prevent candidiasis and other mouth infections. Also provide meticulous skin care, paying special attention to pressure points and open sites, such as aspiration and I.V.

Incidence is 0.6 to 6.1 cases per 1 million people in the United States. There is no racial predilection.

Complications

- Life-threatening hemorrhage
- Secondary opportunistic infections

Signs and symptoms

Clinical features of aplastic anemias vary with the severity of pancytopenia but develop insidiously in many cases. Anemic symptoms include progressive weakness and fatigue, shortness of breath, headache, pallor and, ultimately, tachycardia and heart failure. Thrombocytopenia leads to

ecchymosis, petechiae, and hemorrhage, especially from the mucous membranes (nose, gums, rectum, and vagina) or into the retina or central nervous system. Neutropenia may lead to infection (fever, oral and rectal ulcers, and sore throat) but without characteristic inflammation.

Diagnosis

Confirmation of aplastic anemia requires a series of laboratory tests:

- RBCs are usually normochromic and normocytic (although macrocytosis [larger-than-normal erythrocytes] and anisocytosis [excessive variation in erythrocyte size] may exist), with a total count of 1 million/µl or less. Absolute reticulocyte count is very low.
- Serum iron level is elevated (unless bleeding occurs), but total iron-binding capacity is normal or slightly reduced. Hemosiderin (a derivative of hemoglobin [Hb]) is present, and tissue iron storage is visible microscopically.
- Platelet, neutrophil, and white blood cell counts fall.
- Coagulation tests (bleeding time), reflecting decreased platelet count, are abnormal.
- Bone marrow aspiration from several sites may yield a “dry tap,” and biopsy will show severely hypocellular or aplastic marrow, with varied amounts of fat, fibrous tissue, or gelatinous replacement; absence of tagged iron (because iron is deposited in the liver rather than bone marrow) and megakaryocytes (platelet precursors); and depression of erythroid elements.

Differential diagnosis must rule out paroxysmal nocturnal hemoglobinuria and other diseases in which pancytopenia is common.

Treatment

Effective treatment must eliminate any identifiable cause and provide vigorous supportive measures, such as packed RBC, platelet, and experimental histocompatibility locus antigen-matched leukocyte transfusions. Even after elimination of the cause, recovery can take

months. Bone marrow transplantation is the treatment of choice for anemia due to severe aplasia and for patients who need constant RBC transfusions. (See *Bone marrow transplantation*.)

Patients with low leukocyte counts need special measures to prevent infection. The infection itself may require specific antibiotics; however, these aren't given prophylactically because they tend to encourage resistant strains of organisms. Patients with low Hb levels may need respiratory support

with oxygen in addition to blood transfusions.

For older patients, or for those who don't have a matched bone marrow donor, antithymocyte globulin (ATG) is an alternative treatment. ATG is a horse serum that contains antibodies against human T cells. It may be used in an attempt to suppress the body's immune system, allowing the bone marrow to resume its blood cellgenerating function. Other immunosuppressant agents, such as cyclosporine, may also be used.

Other treatments may include corticosteroids to stimulate erythroid production, marrow-stimulating agents such as androgens (which remain controversial), and colony stimulation factors to encourage growth of specific cellular components.

Special considerations

- If the platelet count is low (less than 20,000/µl), prevent bleeding by avoiding I.M. injections, suggesting the use of an electric razor and a soft toothbrush, humidifying oxygen to prevent drying of mucous membranes, avoiding enemas and rectal temperatures, and promoting regular bowel movements through the use of a stool softener and a proper diet to prevent constipation. Also, apply pressure to venipuncture sites until bleeding stops. Detect bleeding early by checking for blood in urine and stool, and assessing skin for petechiae.
- Take safety precautions to prevent falls that could lead to prolonged bleeding or hemorrhage.
- Help prevent infection by washing your hands thoroughly before entering the patient's room, by making sure he's receiving a nutritious

diet (high in vitamins and proteins) to improve his resistance, and by encouraging meticulous mouth and perianal care.

- Watch for life-threatening hemorrhage, infection, adverse effects of drug therapy, or blood transfusion reaction. Make sure routine throat, urine, nose, rectal, and blood cultures are done regularly and correctly to check for infection. Teach the patient to recognize signs of infection, and tell him to report them immediately.
- If the patient has a low Hb level, which causes fatigue, schedule frequent rest periods. Administer oxygen therapy as needed. If blood transfusions are necessary, assess for a transfusion reaction by checking the patient's temperature and watching for the development of other signs and symptoms, such as rash, hives, itching, back pain, restlessness, and shaking chills.
- Reassure and support the patient and his family by explaining the disease and its treatment, particularly if he has recurring acute episodes. Explain the purpose of all prescribed drugs and discuss possible adverse effects, including which ones he should report promptly. Encourage the patient who doesn't require hospitalization to continue his normal lifestyle, with appropriate restrictions (such as regular rest periods), until remission occurs.
- To prevent aplastic anemia, monitor blood studies carefully in the patient receiving anemia-inducing drugs.
- Support efforts to educate the public about the hazards of toxic agents. Tell parents to keep toxic agents out of the reach of children. Encourage people who work with radiation to wear protective clothing and a radiation-detecting badge, and to observe plant safety precautions. Those who work with benzene (solvent) should know that 10 parts per million is the highest safe environmental level and that a delayed reaction to benzene may develop.

Sideroblastic anemias

Sideroblastic anemias are a group of heterogenous disorders with a common defect; they fail to use iron in hemoglobin (Hb) synthesis, despite the availability of adequate iron stores. These anemias may be hereditary or acquired; the acquired form, in turn, can be primary or

secondary. Hereditary sideroblastic anemia commonly responds to treatment with pyridoxine. Correction of the secondary acquired form depends on the causative disorder; the primary acquired (idiopathic) form, however, resists treatment and usually proves fatal within 10 years after onset of complications or a concomitant disease.

Causes and incidence

Hereditary sideroblastic anemia appears to be transmitted by X-linked inheritance, occurring mostly in young males; females are carriers and usually show no signs of this disorder.

The acquired form may be secondary to ingestion of or exposure to toxins, such as alcohol and lead, or to certain drugs. It can also occur as a complication of other diseases, such as rheumatoid arthritis, lupus erythematosus, multiple myeloma, tuberculosis, and severe infections.

The primary acquired form, known as refractory anemia with ringed sideroblasts, is most common in elderly people. It's commonly associated with thrombocytopenia or leukopenia as part of a myelodysplastic syndrome.

In sideroblastic anemia, normoblasts fail to use iron to synthesize Hb. As a result, iron is deposited in the mitochondria of normoblasts, which are then termed ringed sideroblasts.

Complications

- Severe cardiac, hepatic, and pancreatic disease
- Respiratory complications

Signs and symptoms

Sideroblastic anemias usually produce nonspecific clinical effects, which may exist for several years before being identified. Such effects include anorexia, fatigue, weakness, dizziness, pale skin and mucous membranes and, occasionally, enlarged lymph nodes. Heart and liver failure may develop due to excessive iron accumulation in these organs, causing dyspnea, exertional angina, slight jaundice, and hepatosplenomegaly.

Hereditary sideroblastic anemia is associated with increased GI absorption of iron, causing signs of hemosiderosis. Additional symptoms in secondary sideroblastic anemia depend upon the underlying cause.

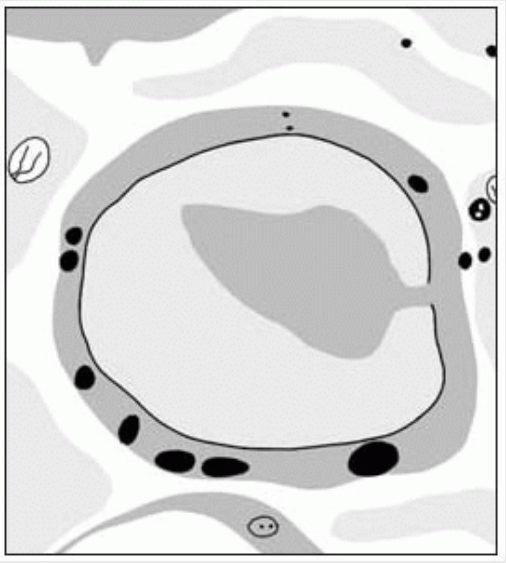
Diagnosis

CONFIRMING DIAGNOSIS

Ringed sideroblasts on microscopic examination of bone marrow aspirate, stained with Prussian blue or alizarin red dye, confirm this diagnosis. (See Ringed sideroblast.)

RINGED SIDEROBLAST

Electron microscopy shows large iron deposits in the mitochondria that surround the nucleus, forming the characteristic ringed sideroblast.



Microscopic examination of blood shows erythrocytes to be hypochromic or normochromic and slightly macrocytic. Red cell precursors may be megaloblastic, with anisocytosis (abnormal variation in red blood cell [RBC] size) and poikilocytosis (abnormal variation in RBC shape). Unlike iron deficiency anemia, sideroblastic anemia lowers Hb levels and raises serum iron and transferrin levels. In turn, faulty Hb production raises urobilinogen and bilirubin levels. Platelets and leukocytes remain normal, but, occasionally, thrombocytopenia or leukopenia occurs.

Treatment

Treatment of sideroblastic anemias depends on the underlying cause. The hereditary form usually responds to several weeks of treatment with high doses of pyridoxine (vitamin B_6). The acquired secondary form generally subsides after the causative drug or toxin is removed, or the underlying condition is adequately treated. Folic acid supplements may also be beneficial when concomitant megaloblastic nuclear changes in RBC precursors are present. Elderly patients with sideroblastic anemia (usually the primary acquired form) are less likely to improve quickly and are more likely to develop serious complications. Deferoxamine may be used to treat chronic iron overload in selected patients.

Carefully crossmatched transfusions (providing needed Hb) or high doses of androgens are effective palliative measures for some patients with the primary acquired form of sideroblastic anemia. However, this form is essentially refractory to treatment and usually leads to death from acute leukemia or from respiratory or cardiac complications.

Some patients with sideroblastic anemia may benefit from phlebotomy to prevent hemochromatosis (the accumulation of iron in body tissues). Phlebotomy steps up the rate of erythropoiesis and uses up excess iron stores; thus, it reduces serum and total-body iron levels.

Special considerations

- Administer medications as indicated. Teach the patient the importance of continuing prescribed therapy, even after he begins to feel better.
- Provide frequent rest periods if the patient becomes easily fatigued.
- If phlebotomy is scheduled, explain the procedure thoroughly to help reduce anxiety. If this procedure must be repeated frequently, provide a high-protein diet to help replace the protein lost during phlebotomy. Encourage the patient to follow a similar diet at home.
- Always inquire about the possibility of exposure to lead in the home (especially for children) or on the job.

- Identify patients who abuse alcohol; refer them for appropriate therapy.

Thalassemia

Thalassemia, a hereditary group of hemolytic anemias, is characterized by defective synthesis in the polypeptide chains necessary for hemoglobin (Hb) production. Consequently, red blood cell (RBC) synthesis is also impaired.

ß-thalassemia is the most common form of this disorder. It results from defective beta polypeptide chain synthesis and occurs in three clinical forms: major, intermedia, and minor. The resulting anemia's severity depends on whether the patient is homozygous or heterozygous for the thalassemic trait. The prognosis for ß-thalassemia varies. People with thalassemia major seldom survive to adulthood; children with thalassemia intermedia develop normally into adulthood, although puberty is usually delayed; people with thalassemia minor can expect a normal life span.

Causes and incidence

Thalassemia major and *thalassemia intermedia* result from homozygous inheritance of the partially dominant autosomal gene responsible for this trait. *Thalassemia minor* results from heterozygous inheritance of the same gene. In these disorders, total or partial deficiency of beta polypeptide chain production impairs Hb synthesis and results in continual production of fetal Hb, lasting even past the neonatal period.

Thalassemia is most common in people of Mediterranean ancestry (especially Italian and Greek) but also occurs in blacks and people from southern China, southeast Asia, and India.

Complications

- Pathological fractures
- Cardiac arrhythmias
- Heart failure

Signs and symptoms

In thalassemia major (also known as *Cooley's anemia, Mediterranean disease,* and *erythroblastic anemia*), the neonate is well at birth but develops severe anemia, bone abnormalities, failure to thrive, and life-threatening complications. (See *Thalassemia major.*) In many cases, the first signs are pallor and yellow skin and scleras in infants ages 3 to 6 months. Later clinical features, in addition to severe anemia, include splenomegaly or hepatomegaly, with abdominal enlargement, frequent infections, bleeding tendencies (especially toward epistaxis), and anorexia.

Children with thalassemia major typically have small bodies and large heads and may also be mentally retarded. Infants may have mongoloid features because bone marrow hyperactivity has thickened the bone at the base of the nose. As these children grow older, they become susceptible to pathologic fractures as a result of expansion of the marrow cavities with thinning of the long bones. They're also subject to cardiac arrhythmias, heart failure, and other complications that result from iron deposits in the heart and in other tissues from repeated blood transfusions.

Thalassemia intermedia comprises moderate thalassemic disorders in homozygotes. Patients with this condition show some degree of anemia, jaundice, and splenomegaly and, possibly, signs of hemosiderosis due to increased intestinal absorption of iron.

Thalassemia minor may cause mild anemia but usually produces no symptoms and is commonly overlooked. It should be differentiated from iron deficiency anemia.

Diagnosis

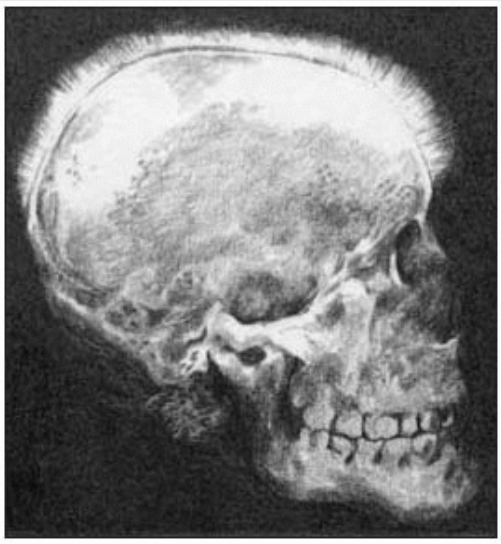
In thalassemia major, laboratory results show lowered RBC count and Hb level, microcytosis, and elevated reticulocyte, bilirubin, and urinary and fecal urobilinogen levels. A low serum folate level indicates increased folate utilization by the hypertrophied bone marrow. A peripheral blood smear reveals target cells, microcytes, pale nucleated RBCs, and marked anisocytosis. X-rays of the skull and long bones show thinning and

widening of the marrow space because of overactive bone marrow. The bones of the skull and vertebrae may appear granular; long bones may show areas of osteoporosis. The phalanges may also be deformed (rectangular or biconvex). Quantitative Hb studies show a significant rise in HbF and a slight increase in HbA_2. Diagnosis must rule out iron deficiency anemia, which also produces hypochromia (slightly lowered Hb level) and microcytic (notably small) RBCs.

In thalassemia intermedia, laboratory results show hypochromia and microcytic RBCs, but the anemia is less severe than that in thalassemia major. In thalassemia minor, laboratory results show hypochromia and microcytic RBCs. Quantitative Hb studies show a significant increase in HbA_2 levels and a moderate rise in HbF levels.

THALASSEMIA MAJOR

X-rays show a characteristic skull abnormality in thalassemia major: diploetic fibers extending from the internal lamina.



Treatment

Treatment of thalassemia major is essentially supportive. For example, infections require prompt treatment with appropriate antibiotics. Folic acid supplements help maintain folic acid levels in the face of increased requirements. Transfusions of packed RBCs raise Hb levels but must be

used judiciously to minimize iron overload. In addition, patients who receive blood transfusions should avoid iron supplements and oxidative drugs because iron levels can become toxic. Those who receive significant numbers of blood transfusions may require chelation therapy to remove iron from the body. Bone marrow transplantation is being investigated as a treatment, with success found mostly in children.

Thalassemia intermedia and thalassemia minor generally don't require treatment.

Iron supplements are contraindicated in all forms of thalassemia.

Special considerations

- During and after RBC transfusions for thalassemia major, watch for adverse reactions —shaking chills, fever, rash, itching, and hives.
- Stress the importance of good nutrition, meticulous wound care, periodic dental checkups, and other measures to prevent infection.
- Discuss with the parents of a young patient various options for healthy physical and creative outlets. Such a child must avoid strenuous athletic activity because of increased oxygen demand and the tendency toward pathologic fractures, but he may participate in less stressful activities.
- Teach parents to watch for signs of hepatitis and iron overload, which are always possible with frequent transfusions.
- Because parents may have questions about the vulnerability of future offspring, refer them for genetic counseling. Also refer adult patients with thalassemia minor and thalassemia intermedia for genetic counseling; they need to recognize the risk of transmitting thalassemia major to their children if they marry another person with thalassemia. If such people choose to marry and have children, their children should be evaluated for thalassemia by age 1. Be sure to tell people with thalassemia minor that their condition is benign.

Iron deficiency anemia

Iron deficiency anemia is caused by an inadequate supply of iron for optimal formation of red blood cells (RBCs), resulting in smaller (microcytic) cells with less color on staining. Body stores of iron, including plasma iron, decrease, as do levels of transferrin, which binds with and transports iron. Insufficient body stores of iron lead to a depleted RBC mass and, in turn, to a decreased hemoglobin (Hb) concentration (hypochromia) and decreased oxygen-carrying capacity of the blood. (See *Absorption and storage of iron.*)

Causes and incidence

Iron deficiency anemia may result from:

- inadequate dietary intake of iron (less than 1 to 2 mg/day), such as in prolonged unsupplemented breast-feeding or bottlefeeding of infants or during periods of stress such as rapid growth in children and adolescents
- iron malabsorption, such as in chronic diarrhea, partial or total gastrectomy, chronic diverticulosis, and malabsorption syndromes, such as celiac disease and pernicious anemia
- blood loss secondary to drug-induced GI bleeding (from anticoagulants, aspirin, and steroids) or due to heavy menses, hemorrhage from trauma, GI ulcers, esophageal varices, or cancer
- pregnancy, which diverts maternal iron to the fetus for erythropoiesis
- intravascular hemolysis-induced hemoglobinuria or paroxysmal nocturnal hemoglobinuria
- mechanical erythrocyte trauma caused by a prosthetic heart valve or vena cava filters.

A common disease worldwide, iron deficiency anemia affects 10% to 30% of the adult population of the United States. It occurs most commonly in premenopausal women, infants (particularly premature or low-birth-weight neonates), children, and adolescents (especially girls). Persons who are at increased risk for iron deficiency include those of low socioeconomic status who don't get a well-balanced diet that includes iron-rich foods.

Complications

- Infection
- Pneumonia
- Pica (in children)
- Bleeding
- Hemochromotosis (from excess iron treatment in children)

Signs and symptoms

Because of the gradual progression of iron deficiency anemia, many patients are initially asymptomatic except for symptoms of any underlying condition. They tend not to seek medical treatment until anemia is severe. At advanced stages, decreased Hb levels and the consequent decrease in the blood's oxygen-carrying capacity cause the patient to develop dyspnea on exertion, fatigue, listlessness, pallor, inability to concentrate, irritability, headache, and a susceptibility to infection. Decreased oxygen perfusion causes the heart to compensate with increased cardiac output and tachycardia.

In chronic iron deficiency anemia, nails become spoon-shaped and brittle, the mouth's corners crack, the tongue turns smooth, and the patient complains of dysphagia or may develop pica. Associated neuromuscular effects include vasomotor disturbances, numbness and tingling of the extremities, and neuralgic pain.

Diagnosis

Blood studies (serum iron levels, total iron-binding capacity, and ferritin levels) and stores in bone marrow may confirm iron deficiency anemia. However, the results of these tests can be misleading because of complicating factors, such as infection, pneumonia, blood transfusion, or iron supplements. Characteristic blood test results include:

- low Hb levels (in males, less than 12 g/dl; in females, less than 10 g/dl)

- low hematocrit (in males, less than 39%; in females, less than 35%)
- low serum iron levels, with high binding capacity
- low serum ferritin levels
- low RBC count, with microcytic and hypochromic cells (in early stages, RBC count may be normal, except in infants and children)
- decreased mean corpuscular Hb in severe anemia.

Bone marrow studies reveal depleted or absent iron stores (done by staining) and normoblastic hyperplasia.

Diagnosis must rule out other forms of anemia, such as those that result from thalassemia minor, cancer, and chronic inflammatory, hepatic, and renal disease.

Treatment

The first priority of treatment is to determine the underlying cause of anemia. Once this is determined, iron replacement therapy can begin. Treatment of choice is an oral preparation of iron or a combination of iron and ascorbic acid (which enhances iron absorption). However, in some cases, iron may have to be administered parenterally —for instance, if the patient is non-compliant to the oral preparation, if he needs more iron than he can take orally, if malabsorption prevents adequate iron absorption, or if a maximum rate of Hb regeneration is desired.

ABSORPTION AND STORAGE OF IRON

Iron, which is essential to erythropoiesis, is abundant throughout the body. Two-thirds of total body iron is found in hemoglobin (Hb); the other third, mostly in the reticuloendothelial system (liver, spleen, bone marrow), with small amounts in muscle, blood serum, and body cells.

Adequate dietary ingestion of iron and recirculation of iron released from disintegrating red cells maintain iron supplies. The duodenum and upper part of the small intestine absorb dietary iron. Such absorption depends

on gastric acid content, the amount of reducing substances (ascorbic acid, for example) present in the alimentary canal, and dietary iron intake. If iron intake is deficient, the body gradually depletes its iron stores, causing decreased Hb levels and, eventually, symptoms of iron deficiency anemia.

Because total dose I.V. infusion of supplemental iron is painless and requires fewer injections, it's usually preferred to I.M. administration. Pregnant patients and geriatric patients with severe anemia, for example, should receive a total dose infusion of iron dextran in normal saline solution over 8 hours. To minimize the risk of an allergic reaction to iron, an I.V. test dose of 0.5 ml should be given first. For more patient care information, see *Supportive management of patients with anemia,* page 516.

Special considerations

- Monitor the patient's compliance with the prescribed iron supplement therapy. Advise the patient not to stop therapy even if he feels better, because replacement of iron stores takes time.
- Tell the patient he may take iron supplements with a meal to decrease gastric irritation. Advise him to avoid fiber, milk, milk products, and antacids because they interfere with iron absorption; however, vitamin C can increase absorption.
- Warn the patient that iron supplements may result in dark green or black stools and can cause constipation.
- Instruct the patient to drink liquid supplemental iron through a straw to prevent staining his teeth.
- Tell the patient to report reactions, such as nausea, vomiting, diarrhea, constipation, fever, or severe stomach pain, which may require a dosage adjustment.

SUPPORTIVE MANAGEMENT OF PATIENTS WITH ANEMIA

To meet the anemic patient's nutritional needs:

- If the patient is fatigued, urge him to eat small, frequent meals throughout the day.
- If the patient has oral lesions, suggest soft, cool, bland foods.
- If the patient has dyspepsia, eliminate spicy foods, and include milk and dairy products in his diet.
- If the patient is anorexic and irritable, encourage his family to bring his favorite foods from home (unless his diet is restricted) and to keep him company during meals, if possible.

To set limitations on activities:

- Assess the effect of a specific activity by monitoring pulse rate during the activity. If the patient's pulse accelerates rapidly and he develops hypotension with hyperpnea, diaphoresis, lightheadedness, palpitations, shortness of breath, or weakness, the activity is too strenuous.
- Tell the patient to pace his activities and to allow for frequent rest periods.

To decrease susceptibility to infection:

- Use strict sterile technique.
- Isolate the patient from infectious persons.
- Instruct the patient to avoid crowds and other sources of infection. Encourage him to practice good hand-washing technique. Stress the importance of receiving necessary immunizations and prompt medical treatment for any sign of infection.

To prepare the patient for diagnostic testing:

- Explain erythropoiesis, the function of blood, and the purpose of diagnostic and therapeutic procedures.

- Tell the patient how he can participate in diagnostic testing. Give him an honest description of the pain or discomfort he will probably experience.
- If possible, schedule all tests to avoid disrupting the patient's meals, sleep, and visiting hours.

To prevent complications:

- Observe for signs of bleeding that may exacerbate anemia. Check stool for occult bleeding. Assess for ecchymoses, gingival bleeding, and hematuria. Monitor vital signs frequently.
- If the patient is confined to strict bed rest, assist with range-of-motion exercises and frequent turning, coughing, and deep breathing.
- If blood transfusions are needed for severe anemia (hemoglobin level less than 5 g/dl), give washed red blood cells, as ordered, in partial exchange if evidence of pump failure is present. Carefully monitor for signs of circulatory overload or transfusion reaction. Watch for a change in pulse rate, blood pressure, or respiratory rate, or onset of fever, chills, pruritus, or edema. If any of these signs develop, stop the transfusion and notify the physician.
- Warn the patient to move about or change positions slowly to minimize dizziness induced by cerebral hypoxia.

HOW TO INJECT IRON SOLUTIONS

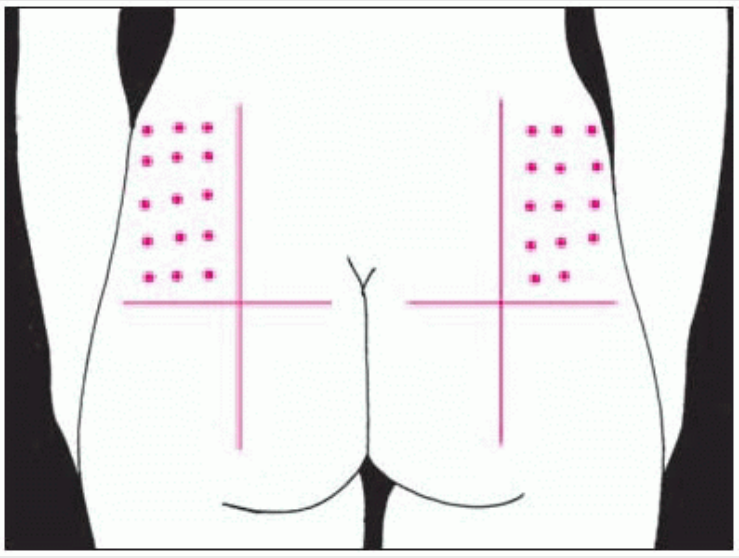
For deep I.M. injections of iron solutions, use the Z-track technique to avoid subcutaneous irritation and discoloration from leaking medication.

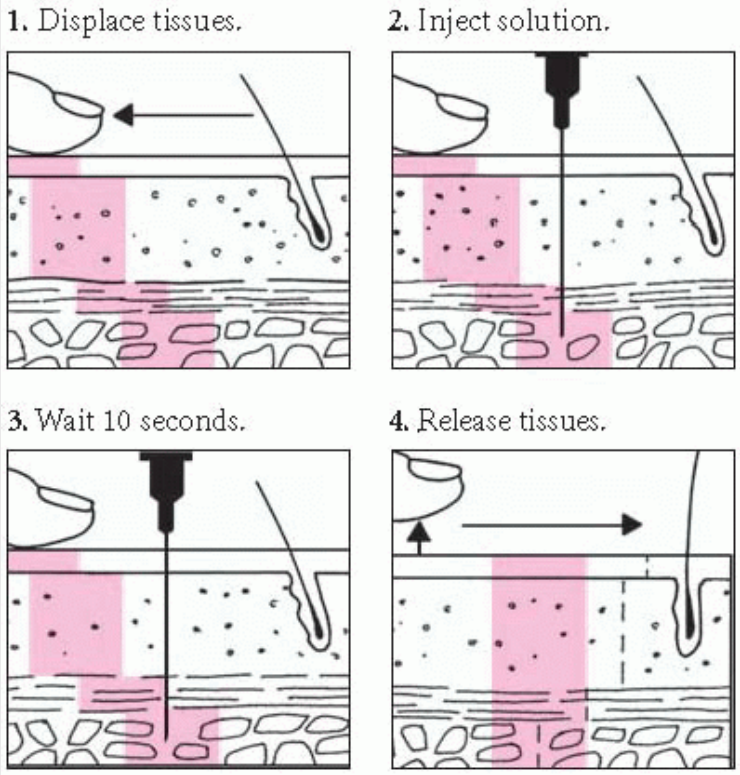
Choose a 19G to 20G, 2” to 3” needle. After drawing up the solution, change to a fresh needle to avoid tracking

the solution through to subcutaneous tissue. Draw 0.5 cc of air into the syringe as an “air lock.”

Displace the skin and fat at the injection site (in the upper outer quadrant of the buttocks or the ventro-gluteal site only) firmly to one side. Clean the area and insert the needle. Aspirate to check for entry into a blood vessel. Inject the solution slowly, followed by the 0.5 cc of air in the syringe. Wait 10 seconds, then pull the needle straight out, and release tissues.

Apply direct pressure to the site but don't massage it. Caution the patient against vigorous exercise for 15 to 30 minutes.





ALERT

If the patient receives I.V. iron, monitor the infusion rate carefully and observe for an allergic reaction. Stop the infusion and begin supportive treatment immediately if the patient shows signs of an adverse reaction. Also, watch for dizziness and headache and for thrombophlebitis around the I.V. site.

- Use the Z-track injection method when administering iron I.M. to prevent skin discoloration, scarring, and irritating iron deposits in the skin. (See *How to inject iron solutions*.)
- Because an iron deficiency may recur, advise regular checkups and blood studies. (See *Preventing iron deficiency anemia*, page 518.)

PREVENTION

PREVENTING IRON DEFICIENCY ANEMIA

Play a vital role in preventing iron deficiency anemia in your patients by encouraging the following actions:

Include iron-rich foods in diet

Teach the basics of a nutritionally balanced diet by having your patients include foods rich in iron, such as those listed below, in their diet.

- Meat (especially liver)
- Egg yolks
- Dried beans or peas
- Green leafy vegetables
- Dried fruits
- Cream of Wheat cereal
- Molasses

Include vitamin C-rich foods in diet

Encourage your patients to consume foods high in vitamin C (ascorbic acid) at the same time they're eating iron-rich foods. The vitamin C aids in the absorption of the iron.These foods are rich in vitamin C:

- Citrus fruit or juice
- Tomatoes
- Broccoli
- Melons
- Strawberries
- Red peppers

Include prophylactic oral iron

Emphasize the need for high-risk individuals, such as premature infants, children younger than age 2, and pregnant women, to receive prophylactic oral iron, as ordered by a physician. (Children younger than age 2

should also receive supplemental cereals and formulas high in iron.)

Assess dietary habits

Assess a family's dietary habits for iron intake and note the influence of childhood eating patterns, cultural food preferences, and family income on adequate nutrition.

Assess medication history

Carefully assess your patients' drug histories because certain drugs, such as pancreatic enzymes and vitamin E, may interfere with iron metabolism and absorption and because aspirin, steroids, and other drugs may cause GI bleeding. (Teach patients who must take medications that are gastric irritants to take these medications with meals or milk.)

POLYCYTHEMIAS

Polycythemia vera

Polycythemia vera is a chronic, myeloproliferative disorder characterized by increased red blood cell (RBC) mass, leukocytosis, thrombocytosis, and increased hemoglobin concentration, with normal or increased plasma volume. This disease is also known as *primary polycythemia*, *erythremia*, *polycythemia rubra vera*, *splenomegalic polycythemia*, and *Vaquez-Osler disease*.

The prognosis depends on the patient's age at diagnosis, the type of treatment used, and complications. Mortality is high if polycythemia is untreated or is associated with leukemia or myeloid metaplasia.

Causes and incidence

In polycythemia vera, uncontrolled and rapid cellular reproduction and maturation cause proliferation or hyperplasia of all bone marrow cells (panmyelosis). The cause of such uncontrolled cellular activity is unknown but it's probably due to a multipotential stem cell defect.

Polycythemia vera usually occurs between ages 40 and 60, most commonly

among males of Jewish ancestry; it seldom affects children or blacks and doesn't appear to be familial.

Complications

- Thrombosis of small vessels
- Ruddy cyanosis of nose
- Clubbing
- Splenomegaly
- Renal calculus formation
- Abdominal thrombosis
- Hemorrhage

Signs and symptoms

Increased RBC mass results in hyperviscosity and inhibits blood flow to microcirculation. Subsequently, increased viscosity, diminished velocity, and thrombocytosis promote intravascular thrombosis. In early stages, polycythemia vera usually produces no symptoms. (Increased hematocrit [HCT] may be an incidental finding.) However, as altered circulation secondary to increased RBC mass produces hypervolemia and hyperviscosity, the patient may complain of a feeling of fullness in the head, headache, dizziness, and other symptoms, depending on the body system affected. The patient may also complain of severe itching after a warm or hot shower. Hyperviscosity may lead to thrombosis of smaller vessels with ruddy cyanosis of the nose and clubbing of the digits.

Paradoxically, hemorrhage is a complication of polycythemia vera. It may be due to defective platelet function or to hyperviscosity and the local effects from excess RBCs exerting pressure on distended venous and capillary walls. (See *Clinical features of polycythemia vera,* page 520.)

Diagnosis

Laboratory studies confirm polycythemia vera by showing increased RBC mass and normal arterial oxygen saturation in association with splenomegaly or two of the following: thrombocytosis, leukocytosis, elevated leukocyte alkaline phosphatase level, or elevated serum vitamin B_{12} level or unbound B_{12}-binding capacity.

Another common finding is increased uric acid production, leading to hyperuricemia and hyperuricuria. Other laboratory results include increased blood histamine levels, decreased serum iron concentration, and decreased or absent urinary erythropoietin. Bone marrow biopsy reveals panmyelosis.

Treatment

Phlebotomy can reduce RBC mass promptly. The frequency of phlebotomy and the amount of blood removed each time depend on the patient's condition. Typically, 350 to 500 ml of blood can be removed every other day until the HCT is reduced to the low-normal range. After repeated phlebotomies, the patient develops iron deficiency, which stabilizes RBC production and reduces the need for phlebotomy. Pheresis permits the return of plasma to the patient, diluting the blood and reducing hypovolemic symptoms.

Phlebotomy doesn't reduce the white blood cell or platelet count and won't control the hyperuricemia associated with marrow cell proliferation. For severe symptoms, myelosuppressive therapy may be used. Chemotherapeutic agents may be used to suppress the bone marrow, but these agents may cause leukemia and should be reserved for older patients and those with problems uncontrolled by phlebotomy. The current preferred myelosuppressive agent is hydroxyurea, which isn't associated with leukemia. Patients who have had previous thrombotic problems should be considered for myelosuppressive therapy. The use of antiplatelet therapy is controversial because it may cause gastric bleeding. Allopurinol may be given for hyperuricemia.

Special considerations

If the patient requires phlebotomy, explain the procedure, and reassure him that it will relieve distressing symptoms. Check blood pressure, pulse rate, and respiratory rate. During phlebotomy, make sure the patient is lying down comfortably to prevent vertigo and syncope. Stay alert for tachycardia, clamminess, or complaints of vertigo. If these effects occur, the procedure should be stopped.

- Immediately after phlebotomy, check blood pressure and pulse rate. Have the patient sit up for about 5 minutes before allowing him to walk; this prevents vasovagal attack or orthostatic hypotension. Also, have him drink 24 oz (710 ml) of juice or water.
- Tell the patient to watch for and report signs or symptoms of iron deficiency (pallor, weight loss, asthenia [weakness], and glossitis).
- Keep the patient active and ambulatory to prevent thrombosis. If bed rest is absolutely necessary, prescribe a daily program of both active and passive range-of-motion exercises.
- Watch for complications: hypervolemia, thrombocytosis, and signs or symptoms of an impending stroke (decreased sensation, numbness, transitory paralysis, fleeting blindness, headache, and epistaxis).
- Regularly examine the patient closely for bleeding. Tell him which are the most common bleeding sites (such as the nose, gingiva, and skin) so he can check for bleeding. Advise him to report any abnormal bleeding promptly.
- To compensate for increased uric acid production, give additional fluids, administer allopurinol, and alkalinize the urine to prevent uric acid calculi.
- If the patient has symptom-producing splenomegaly, suggest or provide small, frequent meals, followed by a rest period, to prevent nausea and vomiting.
- Report acute abdominal pain immediately; it may signal splenic infarction, renal calculi, or abdominal organ thrombosis.

During myelosuppressive treatment:

- Monitor complete blood count and platelet count before and during therapy. Warn the outpatient who develops leukopenia that his resistance to infection is low; advise him to avoid crowds and watch for the symptoms of infection. If leukopenia develops in a hospitalized patient who needs reverse isolation, follow hospital guidelines. If thrombocytopenia develops, tell the patient to watch for signs of bleeding (blood in urine, nosebleeds, and black stool).
- Tell the patient about possible reactions (nausea, vomiting, and risk of infection) to alkylating agents. Alopecia may follow the use of busulfan, cyclophosphamide, and uracil mustard; sterile hemorrhagic cystitis may follow the use of cyclophosphamide (forcing fluids can prevent it). Watch for and report all reactions. If nausea and vomiting occur, begin antiemetic therapy and adjust the patient's diet.

CLINICAL FEATURES OF POLYCYTHEMIA VERA

Signs and symptoms	Causes
Eye, ear, nose, and throat	
▪ Visual disturbances (blurring, diplopia, scotoma, engorged veins of fundus and retina) and congestion of conjunctiva, retina, retinal veins, oral mucous membrane	▪ Hypervolemia and hyperviscosity
▪ Epistaxis or gingival bleeding	▪ Engorgement of capillary beds
Central nervous system	
▪ Headache or fullness in the head, lethargy, weakness, fatigue, syncope, tinnitus, paresthesia of digits, and impaired mentation	▪ Hypervolemia and hyperviscosity
Cardiovascular system	
▪ Hypertension	▪ Hypervolemia and hyperviscosity
▪ Intermittent claudication, thrombosis and emboli,	▪ Hypervolemia, thrombocytosis,

angina, thrombophlebitis	and vascular disease
▪ Hemorrhage	▪ Engorgement of capillary beds
Skin	
▪ Pruritus (especially after hot bath)	▪ Basophilia (secondary histamine release)
▪ Urticaria	▪ Altered histamine metabolism
▪ Ruddy cyanosis	▪ Hypervolemia and hyperviscosity due to congested vessels, increased oxyhemoglobin, and reduced hemoglobin
▪ Night sweats	▪ Hypermetabolism
▪ Ecchymosis	▪ Hemorrhage
GI system	
▪ Epigastric distress	▪ Hypervolemia and hyperviscosity
▪ Early satiety and fullness	▪ Hepatosplenomegaly
▪ Peptic ulcer pain	▪ Gastric thrombosis and hemorrhage
▪ Hepatosplenomegaly	▪ Congestion, extramedullary hemopoiesis, and myeloid metaplasia
▪ Weight loss	▪ Hypermetabolism
Respiratory system	
▪ Dyspnea	▪ Hypervolemia and hyperviscosity
Musculoskeletal system	

▪ Joint symptoms	▪ Increased urate production secondary to nucleoprotein turnover

Spurious polycythemia

Spurious polycythemia, also known as *relative polycythemia, stress erythrocytosis, stress polycythemia, benign polycythemia, Gaisböck's syndrome,* and *pseudopolycythemia,* is characterized by increased hematocrit (HCT) and normal or decreased red blood cell (RBC) total mass; it results from decreasing plasma volume and subsequent hemoconcentration.

Causes and incidence

There are three possible causes of spurious polycythemia:

- Dehydration—Conditions that promote severe fluid loss decrease plasma levels and lead to hemoconcentration. Such conditions include persistent vomiting or diarrhea, burns, adrenocortical insufficiency, aggressive diuretic therapy, decreased fluid intake, diabetic acidosis, and renal disease.
- Hemoconcentration due to stress— Nervous stress leads to hemoconcentration by some unknown mechanism (possibly by temporarily decreasing circulating plasma volume or vascular redistribution of erythrocytes). This form of erythrocytosis (chronically elevated HCT) is particularly common in the middle-aged man who's a chronic smoker and a type A personality (tense, hard driving, and anxious).
- High normal RBC mass and low normal plasma volume—In many patients, an increased HCT merely reflects a normally high RBC mass and low plasma volume. This is particularly common in patients who don't smoke, aren't obese, and have no history of hypertension.

Other factors that may be associated with spurious polycythemia include hypertension, thromboembolitic disease, elevated serum cholesterol and uric acid levels, and familial tendency. It usually affects middle-aged people and occurs more commonly in men than in women.

Complications

- Hypercholesterolemia
- Hyperlipidemia
- Hyperuricemia

Signs and symptoms

The patient with spurious polycythemia usually has no specific symptoms but may have vague complaints, such as headaches, dizziness, and fatigue. Less commonly, he may develop diaphoresis, dyspnea, and claudication.

Typically, the patient has a ruddy appearance, a short neck, slight hypertension, and a tendency to hypoventilate when recumbent.

He shows no associated hepatosplenomegaly but may have cardiac or pulmonary disease.

Diagnosis

Hemoglobin levels, HCT, and RBC count are elevated; RBC mass, arterial oxygen saturation, and bone marrow are normal. Plasma volume may be decreased or normal. Hypercholesterolemia, hyperlipidemia, or hyperuricemia may be present.

CONFIRMING DIAGNOSIS

Spurious polycythemia is distinguishable from true polycythemia vera by its characteristic normal RBC mass, elevated HCT, and the absence of leukocytosis.

Treatment

The principal goals of treatment are to prevent life-threatening thromboembolism and to correct dehydration. Rehydration with appropriate fluids and electrolytes is the primary therapy for spurious polycythemia secondary to dehydration. Therapy must also include appropriate measures to prevent continuing fluid loss.

Special considerations

- During rehydration, carefully monitor intake and output to maintain fluid and electrolyte balance.
- Whenever appropriate, suggest counseling about the patient's work habits and lack of relaxation. If the patient smokes, make sure he understands how important it is that he stop. Refer him to a smoking-cessation program if necessary.
- Emphasize the need for follow-up examinations every 3 to 4 months after leaving the hospital.
- Thoroughly explain spurious polycythemia, diagnostic measures, and therapy. The hard-driving person predisposed to spurious polycythemia is likely to be more inquisitive and anxious than the average patient. Answer questions honestly, but take care to reassure him that he can effectively control symptoms by complying with the prescribed treatment.

PREVENTION

To prevent thromboemboli in predisposed patients, suggest regular exercise and a lowcholesterol diet. Antilipemics may also be necessary. Reduced calorie intake may be required for the obese patient.

Secondary polycythemia

Secondary polycythemia (also called *reactive polycythemia*) is a disorder characterized by excessive production of circulating red blood cells (RBCs) due to hypoxia, tumor, or disease.

Causes and incidence

Secondary polycythemia may result from increased production of erythropoietin. This hormone, which is possibly produced and secreted in the kidneys, stimulates bone marrow production of RBCs. Increased production may be a compensatory physiologic response to hypoxemia, which may result from:

- chronic obstructive pulmonary disease
- hemoglobin (Hb) abnormalities (such as carboxyhemoglobinemia, which is seen in heavy smokers)
- heart failure (causing a decreased ventilation-perfusion ratio)
- right-to-left shunting of blood in the heart (as in transposition of the great vessels)
- central or peripheral alveolar hypoventilation (as in barbiturate intoxication or pickwickian syndrome)
- low oxygen content at high altitudes.

Increased production of erythropoietin may also be an inappropriate (pathologic) response to renal disease (such as renal vascular impairment, renal cysts, or hydronephrosis), to central nervous system disease (such as encephalitis and parkinsonism), to neoplasms (such as renal tumors, uterine myomas, or cerebellar hemangiomas), or to endocrine disorders (such as Cushing's syndrome, Bartter's syndrome, or pheochromocytomas). Rarely, secondary polycythemia results from a recessive genetic trait.

Secondary polycythemia occurs in about 2 out of every 100,000 people living at or near sea level; incidence rises among those living at high altitudes.

Complications

- Hemorrhage
- Thromboemboli

Signs and symptoms

In the hypoxic patient, suggestive physical findings include ruddy cyanotic skin, emphysema, and hypoxemia without hepatosplenomegaly or hypertension. Clubbing of the fingers may occur if the underlying disease is cardiovascular. When secondary polycythemia isn't caused by hypoxemia, it's usually an incidental finding during treatment of an underlying disease.

Diagnosis

CONFIRMING DIAGNOSIS

Laboratory values for secondary polycythemia include increased RBC mass (increased hematocrit, Hb levels, and mean corpuscular volume and mean corpuscular Hb values) and urinary erythropoietin and blood histamine levels, with decreased or normal arterial oxygen saturation. Bone marrow biopsies reveal hyperplasia confined to the erythroid series.

Unlike polycythemia vera, secondary polycythemia isn't associated with leukocytosis or thrombocytosis.

Treatment

The goal of treatment is correction of the underlying disease or environmental condition. In severe secondary polycythemia in which altitude is a contributing factor, relocation may be advisable. If secondary polycythemia has produced hazardous hyperviscosity or if the patient doesn't respond to treatment of the primary disease, reduction of blood volume by phlebotomy or pheresis may be effective. Emergency phlebotomy is indicated for prevention of impending vascular occlusion or before emergency surgery. In the latter case, it's usually advisable to remove excess RBCs and reinfuse the patient's plasma.

ALERT

Because a patient with polycythemia has an increased risk of hemorrhage during and after surgery, elective surgery should be avoided until polycythemia is controlled.

Typically, secondary polycythemia disappears when the primary disease is corrected.

Special considerations

- Keep the patient as active as possible to decrease the risk of thrombosis due to increased blood viscosity.
- Reduce calorie and sodium intake to counteract the tendency toward hypertension.
- Before and after phlebotomy, check blood pressure with the patient lying down. After the procedure, have the patient drink 24 oz (710 ml) of water or juice. To prevent syncope, have him sit upright for about 5 minutes before walking.
- Emphasize the importance of regular blood studies (every 2 to 3 months), even after the disease is controlled.
- Teach the patient and his family about the underlying disorder. Help them understand its relationship to polycythemia and the measures needed to control both.
- Teach the patient to recognize symptoms of recurring polycythemia and the importance of reporting them promptly.

HEMORRHAGIC DISORDERS

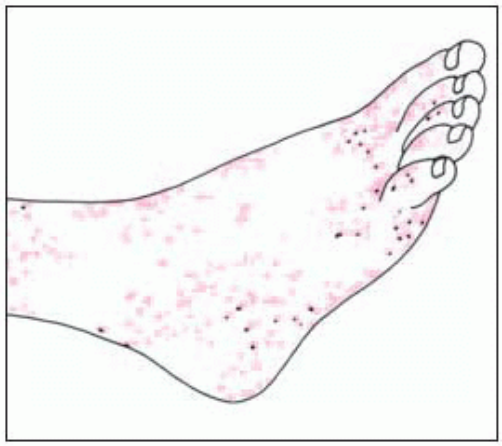
Allergic purpuras

Allergic purpura, a nonthrombocytopenic purpura, is an acute or chronic vascular inflammation affecting the skin, joints, and GI and genitourinary (GU) tracts, in association with allergy symptoms. When allergic purpura primarily affects the GI tract, with accompanying joint pain, it's called *Henoch-Schönlein syndrome,* or *anaphylactoid purpura.* However, the term *allergic purpura* applies to purpura associated with many other conditions such as erythema nodosum. An acute attack of allergic purpura can last for several weeks and is potentially fatal (usually from renal failure); however, most patients do recover.

Fully developed allergic purpura is persistent and debilitating, possibly leading to chronic glomerulonephritis (especially following a streptococcal infection).

PURPURIC LESIONS

Lesions of allergic purpura, such as those pictured on the foot and leg below, characteristically vary in size.



Causes and incidence

The most common identifiable cause of allergic purpura is probably an autoimmune reaction directed against vascular walls, triggered by a bacterial infection (particularly streptococcal infection). Typically, upper respiratory tract infection occurs 1 to 3 weeks before the onset of symptoms. Other possible causes include allergic reactions to some drugs and vaccines, to insect bites, and to some foods (such as wheat, eggs, milk, and chocolate).

Allergic purpura affects more males than females and is most prevalent in children ages 3 to 7. The prognosis is more favorable for children than adults.

Complications

- Renal failure
- Acute glomerulonephritis

Signs and symptoms

Characteristic skin lesions of allergic purpura are purple, macular, ecchymotic, and of varying size. They're caused by vascular leakage into the skin and mucous membranes. (See *Purpuric lesions*.) The lesions

usually appear in symmetric patterns on the arms, legs, and buttocks and are accompanied by pruritus, paresthesia and, occasionally, angioneurotic edema. In children, skin lesions are generally urticarial and expand and become hemorrhagic. Scattered petechiae may appear on the legs, buttocks, and perineum.

Henoch-Schönlein syndrome commonly produces transient or severe colic, tenesmus (spasmodic contraction of the anal sphincter) and constipation, vomiting, and edema or hemorrhage of the mucous membranes of the bowel, resulting in GI bleeding, occult blood in the stool and, possibly, intussusception. Such GI abnormalities may *precede* overt, cutaneous signs of purpura. Musculoskeletal symptoms, such as rheumatoid pains and periarticular effusions, mostly affect the legs and feet.

In 25% to 50% of patients, allergic purpura is associated with GU signs and symptoms: nephritis; renal hemorrhages that may cause microscopic hematuria and disturb renal function; bleeding from the mucosal surfaces of the ureters, bladder, or urethra; and, occasionally, glomerulonephritis. Also possible are moderate and irregular fever, headache, anorexia, and localized edema of the hands, feet, or scalp.

Diagnosis

No laboratory test clearly identifies allergic purpura (although white blood cell count and erythrocyte sedimentation rate are elevated). Diagnosis therefore necessitates careful clinical observation, in many cases during the second or third attack. Except for a positive tourniquet test (a test to assess the capillaries' ability to withstand increased pressure), coagulation and platelet function tests are usually normal. Small-bowel X-rays may reveal areas of transient edema; in many cases, tests for blood in the urine and stool are positive. Increased blood urea nitrogen and creatinine levels may indicate renal involvement. Diagnosis must rule out other forms of nonthrombocytopenic purpura.

Treatment

Treatment is generally symptomatic; for example, severe allergic purpura may require steroids to relieve edema and analgesics to relieve joint and abdominal pain. Some patients with chronic renal disease may

benefit from immunosuppressive therapy with azathioprine along with identification

of the provocative allergen. *An accurate allergy history is essential.*

Special considerations

- Encourage maintenance of an elimination diet to help identify specific allergenic foods so these foods can be eliminated from the patient's diet.
- Monitor skin lesions and level of pain. Provide analgesics as needed.
- Watch carefully for complications: GI and GU tract bleeding, edema, nausea, vomiting, headache, hypertension (with nephritis), abdominal rigidity and tenderness, and absence of stool (with intussusception).
- To prevent muscle atrophy in the bedridden patient, provide passive or active range-of-motion exercises.
- Provide emotional support and reassurance, especially if the patient is temporarily disfigured by florid skin lesions.
- After the acute stage, stress the need for the patient to *immediately* report *any* recurrence of symptoms (recurrence is most common about 6 weeks after initial onset) and to return for follow-up urinalysis as scheduled.

Hereditary hemorrhagic telangiectasia

Hereditary hemorrhagic telangiectasia (also called *Osler-Weber-Rendu syndrome*) is an inherited vascular disorder in which venules and capillaries dilate and form fragile masses of thin convoluted vessels (telangiectases), resulting in an abnormal tendency to hemorrhage. This disorder affects both sexes but may cause less severe bleeding in girls and women.

Complication

- Secondary iron deficiency anemia

Causes and incidence

Hereditary hemorrhagic telangiectasia is transmitted by autosomal dominant inheritance. It seldom skips generations. In its homozygous state, it may be lethal. It affects 1 in 5,000 to 1 in 10,000 people worldwide.

Signs and symptoms

Signs of hereditary hemorrhagic telangiectasia are present in childhood but increase in severity with age. Localized aggregations of dilated capillaries appear on the skin of the face, ears, scalp, hands, arms, and feet; under the nails; and on the mucous membranes of the nose, mouth, and stomach. These dilated capillaries cause frequent epistaxis, hemoptysis, and GI bleeding, possibly leading to iron deficiency anemia. (In children, epistaxis is usually the first symptom.)

Characteristic telangiectases are violet, bleed spontaneously, may be flat or raised, blanch on pressure, and are nonpulsatile. They may be associated with vascular malformations such as arteriovenous fistulas. Visceral telangiectases are common in the liver, bladder, respiratory tract, and stomach. The type and distribution of these lesions are generally similar among family members.

Generalized capillary fragility, as evidenced by spontaneous bleeding, petechiae, ecchymoses, and spider hemangiomas of varying sizes, may exist without overt telangiectasia. (See *Typical lesions of hereditary hemorrhagic telangiectasia,* page 526.) Rarely, vascular malformation may cause pulmonary arteriovenous fistulas; then, shunting of blood through the fistulas may lead to hypoxemia, recurring cerebral embolism, brain abscess, and clubbing of digits.

Diagnosis

Diagnosis is based principally on an established familial pattern of bleeding disorders and on clinical evidence of telangiectasia and hemorrhage. Bone marrow aspiration demonstrating depleted iron stores confirms secondary iron deficiency anemia. Hypochromic, microcytic anemia is common; abnormal platelet function may also be found.

Coagulation tests are essentially irrelevant, however, because hemorrhage in telangiectasia results from weakness in the vascular wall.

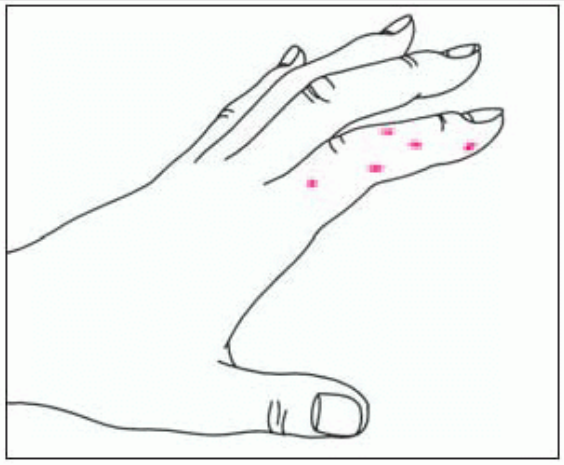
Treatment

Supportive therapy includes blood transfusions for acute hemorrhage and supplemental iron administration to replace iron

lost in repeated mucosal bleeding. Ancillary treatments consist of applying pressure and topical hemostatic agents to bleeding sites, cauterizing bleeding sites not readily accessible, and protecting the patient from trauma and unnecessary bleeding. An interventional radiologist may clot off large collections of abnormal blood vessels in the lungs, called *arteriovenous malformations*, by using a coiling procedure.

TYPICAL LESIONS OF HEREDITARY HEMORRHAGIC TELANGIECTASIA

Dilated capillaries, either flat or raised, appear in localized aggregations, as on the fingers.



On the face, spider hemangiomas reflect capillary fragility.

Parenteral administration of supplemental iron enhances absorption to maintain adequate iron stores and prevents gastric irritation. Administering antipyretics or antihistamines before blood transfusions, and using saline-washed cells, frozen blood, or other types of leukocyte-poor blood instead of whole blood may prevent febrile transfusion reactions.

The administration of estrogen has proved effective in some patients, especially when used to control epistaxis.

Special considerations

ALERT

During the first 15 minutes of a blood transfusion, stay with the patient to watch for adverse reactions. Afterward, check again every 15 minutes for signs and symptoms of a febrile or an allergic transfusion reaction (flushing, shaking chills, fever, headache, rash, tachycardia, and hypertension) because patients with this disorder are quite susceptible to this type of reaction.

- Observe the patient for indications of GI bleeding, such as hematemesis and melena. Instruct him to watch for and report such signs as well.

- If the patient requires an iron supplement, stress the importance of following dosage instructions and of taking oral iron with meals to minimize gastric irritation. Warn him that iron turns stools dark green or black and may cause constipation.
- Provide emotional and psychological support. Encourage the patient to express concerns he may have about his disease and its treatment. As much as possible, include him in care decisions.
- Encourage fluid intake, when possible, if the patient is experiencing a bleeding episode or is hypovolemic. Monitor intake and output.
- Provide good skin care and hygiene, and use sterile technique when caring for the patient. Lesions bleed easily, which may result in infection and skin breakdown.

- Monitor the patient's organ function through physical examination and the comparison of laboratory tests to detect renal, hepatic, or respiratory failure.
- Teach the patient and his family how to manage minor bleeding episodes, especially recurrent epistaxis, and how to recognize major episodes that necessitate emergency intervention.
- Teach the patient and his family about the disease's hereditary nature. Refer him for genetic counseling, as appropriate, and to the Hereditary Hemorrhagic Telangiectasia Foundation International for support and information.

Thrombocytopenia

The most common cause of hemorrhagic disorders, thrombocytopenia is characterized by deficiency of circulating platelets. Because platelets play a vital role in coagulation, this disease poses a serious threat to hemostasis. (See *What happens in thrombocytopenia,* pages 528 and 529.) The prognosis is excellent in drug-induced thrombocytopenia if the offending drug is withdrawn; in such cases, recovery may be immediate. In other types, the prognosis depends on the patient's response to treatment of the underlying cause.

Causes

Thrombocytopenia may be congenital or acquired; the acquired form is more common. In either case, it usually results from decreased or defective production of platelets in the marrow (such as occurs in leukemia, aplastic anemia, or toxicity with certain drugs) or from increased destruction outside the marrow caused by an underlying disorder (such as cirrhosis of the liver, disseminated intravascular coagulation, or severe infection). Less commonly, it results from sequestration (hypersplenism and hypothermia) or platelet loss. Acquired thrombocytopenia may result from certain drugs, such as sulfonamides, antibiotics, gold salts, estrogens, or chemotherapeutic agents. (See *Causes of decreased circulating platelets,* page 530.)

ELDER TIP

In older adults, platelet characteristics change. Granular constituents decrease and plateletrelease factors increase. These changes may reflect diminished bone marrow and increased fibrinogen levels.

An idiopathic form of thrombocytopenia commonly occurs in children. A transient form may follow viral infection (such as Epstein-Barr virus or infectious mononucleosis).

Complication

- Acute hemorrhage

Signs and symptoms

Thrombocytopenia typically produces a sudden onset of petechiae or ecchymoses in the skin or bleeding into any mucous membrane. Nearly all patients are otherwise asymptomatic, although some may complain of malaise, fatigue, and general weakness. In adults, large, blood-filled bullae characteristically appear in the mouth. In severe thrombocytopenia, hemorrhage may lead to tachycardia, shortness of breath, loss of consciousness, and death.

Diagnosis

Diagnosis is based on the results of the patient history (especially a drug history), physical examination, and laboratory tests. Coagulation tests reveal a decreased platelet count (in adults, less than 100,000/µl), prolonged bleeding time (although this doesn't always indicate platelet quality) and normal prothrombin time and partial thromboplastin time. If increased destruction of platelets is causing thrombocytopenia, bone marrow studies will reveal a greater number of megakaryocytes (platelet precursors) and shortened platelet survival (several hours or days rather than the usual 7 to 10 days).

Treatment

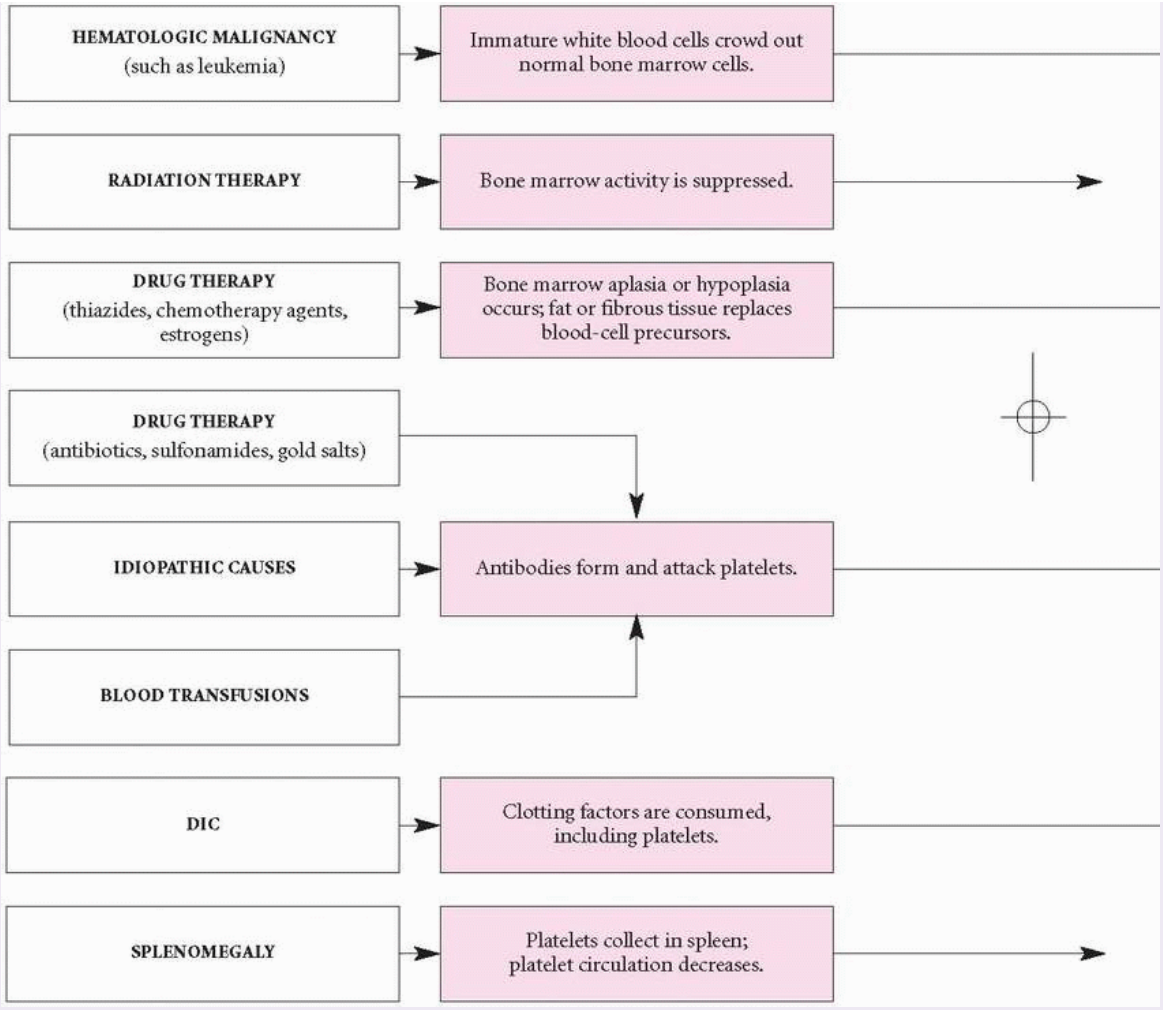
Treatment varies with the underlying cause and may include corticosteroids or immune globulin to increase platelet production. The treatment of choice is removal of the offending agents in drug-induced thrombocytopenia or treatment of the underlying cause. Platelet transfusions are

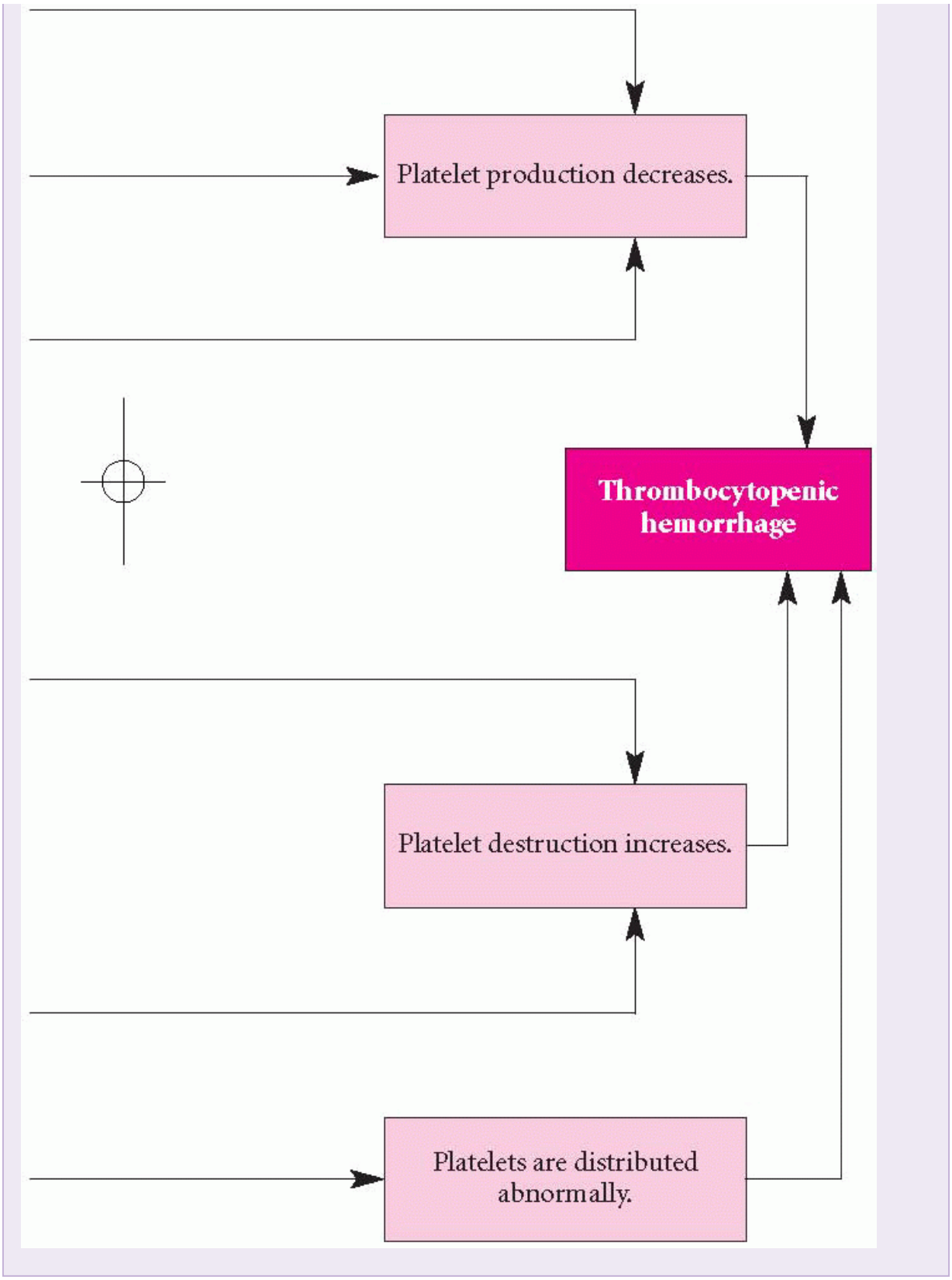
helpful only in treating complications of severe hemorrhage.

PATHOPHYSIOLOGY

WHAT HAPPENS IN THROMBOCYTOPENIA

Thrombocytopenia is the most common cause of bleeding disorders and is characterized by a severe decrease in platelets. This platelet decrease can result from hematologic malignancy, radiation or drug therapy, idiopathic causes, blood transfusions, disseminated intravascular coagulation (DIC), or splenomegaly. Excessive hemorrhaging can lead to shock if interventions are delayed. This chart shows how these conditions and treatments develop into thrombocytopenic hemorrhage.


HEMATOLOGIC MALIGNANCY
(such as leukemia)
Immature white blood cells crowd out normal bone marrow cells.
RADIATION THERAPY
Bone marrow activity is suppressed.
DRUG THERAPY
(thiazides, chemotherapy agents, estrogens)
Bone marrow aplasia or hypoplasia occurs; fat or fibrous tissue replaces blood-cell precursors.
DRUG THERAPY
(antibiotics, sulfonamides, gold salts)
IDIOPATHIC CAUSES
Antibodies form and attack platelets.
BLOOD TRANSFUSIONS
DIC
Clotting factors are consumed, including platelets.
SPLENOMEGALY
Platelets collect in spleen; platelet circulation decreases.


Platelet production decreases.
Thrombocytopenic hemorrhage
Platelet destruction increases.
Platelets are distributed abnormally.

Special considerations

When caring for the patient with thrombocytopenia, take every possible precaution against bleeding.

- Protect the patient from trauma. Keep the side rails up and pad them, if possible. Promote the use of an electric razor and a soft toothbrush. Avoid invasive procedures, such as venipuncture or urinary catheterization, if possible. When venipuncture is unavoidable, be sure to exert pressure on the puncture site for at least 20 minutes or until the bleeding stops.
- Monitor platelet count daily. A 1- to 2-hour postplatelet count will aid assessment of response.
- Test stool for guaiac; dipstick urine and vomitus for blood.
- Watch for bleeding (petechiae, ecchymoses, surgical or GI bleeding, and menorrhagia).
- Warn the patient to avoid aspirin in any form and other drugs that impair coagulation. Teach him how to recognize aspirin or ibuprofen compounds on labels of over-the-counter remedies.
- Advise the patient to avoid straining at stool or coughing, as both can lead to increased intracranial pressure, possibly causing cerebral hemorrhage in the patient with thrombocytopenia. Provide a stool softener to avoid constipation.
- During periods of active bleeding, maintain the patient on strict bed rest if necessary.
- When administering platelet concentrate, remember that platelets are extremely fragile, so infuse them quickly. Don't give platelets to a patient with a fever.

ALERT

During platelet transfusion, monitor the patient for febrile reaction (flushing, chills, fever, headache, tachycardia, and hypertension).

- Histocompatibility locus antigen-typed platelets may be ordered to prevent febrile reaction. A patient with a history of minor reactions may benefit from acetaminophen and diphenhydramine before transfusion.

- If thrombocytopenia is drug-induced, stress the importance of avoiding the offending drug.
- If the patient must receive long-term steroid therapy, teach him to watch for and report cushingoid signs (acne, moon face, hirsutism, buffalo hump, hypertension, girdle obesity, thinning arms and legs, glycosuria, and edema). Emphasize that steroid doses must be discontinued gradually. During steroid therapy, monitor fluid and electrolyte balance, and watch for infection, pathologic fractures, and mood changes.

CAUSES OF DECREASED CIRCULATING PLATELETS

Diminished or defective platelet production

Congenital

- Wiskott-Aldrich syndrome
- Maternal ingestion of thiazides
- Neonatal rubella
- Polycythemia

Acquired

- Aplastic anemia
- Marrow infiltration (acute and chronic leukemias, tumor)
- Nutritional deficiency (B12, folic acid)
- Myelosuppressive agents
- Drugs that directly influence platelet production (thiazides, alcohol, hormones)
- Radiation
- Viral infections (measles, dengue)

Increased peripheral platelet destruction

Congenital

- Nonimmune (prematurity, erythroblastosis fetalis, infection)
- Immune (drug sensitivity, maternal ITP).

Acquired

- Nonimmune (infection, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura)
- Immune (drug-induced, especially with quinine and quinidine; post-transfusion purpura; acute and chronic ITP; sepsis; alcohol)
- Invasive lines and devices
- Intra-aortic balloon pump
- Prosthetic heart valves
- Heparin

Platelet sequestration

- Hypersplenism
- Hypothermia

Platelet loss

- Hemorrhage
- Extracorporeal perfusion

Idiopathic thrombocytopenic purpura

Idiopathic thrombocytopenic purpura (ITP), thrombocytopenia that results from immunologic platelet destruction, may be acute (postviral thrombocytopenia) or chronic (Werlhof's disease, purpura hemorrhagica, essential thrombocytopenia, and autoimmune thrombocytopenia). The prognosis for acute ITP is excellent; nearly four out of five patients recover without treatment. The prognosis for chronic ITP is good; remissions lasting weeks or years are common, especially among women.

Causes and incidence

ITP may be an autoimmune disorder, because antibodies that reduce the life span of platelets have been found in nearly all patients. The spleen probably helps to remove platelets modified by the antibody. Acute ITP usually follows a viral infection, such as rubella or chickenpox, and can follow immunization with a live virus vaccine. Chronic ITP seldom follows infection and is commonly linked to immunologic disorders such as systemic lupus erythematosus. It's also linked to drug reactions. ITP frequently occurs in patients who have abused alcohol, heroin, or morphine, and in patients with acquired immunodeficiency syndrome who are exposed to the rubella virus.

Acute ITP usually affects children between ages 2 and 6; chronic ITP mainly affects

adults younger than age 50, especially women between ages 20 and 40.

Complications

- Cerebral hemorrhage
- Fatal purpuric lesions in vital organs

Signs and symptoms

Clinical features of ITP common to all forms of thrombocytopenia include petechiae, ecchymoses, and mucosal bleeding from the mouth, nose, or GI tract. Generally, hemorrhage is a rare physical finding. Purpuric lesions may occur in vital organs, such as the lungs, kidneys, or brain, and may prove fatal. In acute ITP, which commonly occurs in children, onset is usually sudden, causing easy bruising, epistaxis, and bleeding gums. Onset of chronic ITP is insidious.

Diagnosis

Platelet count less than 20,000/µl and prolonged bleeding time suggest ITP. Platelet size and morphologic appearance may be abnormal; anemia may be present if bleeding has occurred. As in thrombocytopenia, bone marrow studies show an abundance of megakaryocytes and a shortened

circulating platelet survival time (hours or days). Occasionally, platelet antibodies may be found in vitro, but this diagnosis is usually inferred from platelet survival data and the absence of an underlying disease.

Treatment

Acute ITP may be allowed to run its course without intervention or may be treated with glucocorticoids or immune globulin. For chronic ITP, corticosteroids may be the initial treatment of choice. Patients who fail to respond within 1 to 4 months or who need high steroid dosage are candidates for splenectomy, which may be successful in 50% of cases. Alternative treatments include immunosuppression, high-dose gamma globulin injections, and immunoabsorption apheresis using staphylococcal protein-A columns, which filter antibodies out of the bloodstream. Anti-RhD therapy can also be useful in people with specific blood types.

Before splenectomy, the patient may require blood, blood components, and vitamin K to correct anemia and coagulation defects. After splenectomy, he may need blood and component replacement and platelet concentrate. Normally, platelets increase spontaneously after splenectomy.

Special considerations

Patient care for ITP is essentially the same as for other types of thrombocytopenia, with emphasis on teaching the patient to observe for petechiae, ecchymoses, and other signs of recurrence. Monitor patients receiving immunosuppressants for signs of bone marrow depression, infection, mucositis, GI ulcers, and severe diarrhea or vomiting. Tell the patient to avoid aspirin, ibuprofen, and warfarin, as these drugs interfere with platelet function and blood clotting.

Platelet function disorders

Platelet function disorders are similar to thrombocytopenia but result from platelet dysfunction rather than platelet deficiency. They characteristically cause defects in platelet adhesion or procoagulation activity (ability to bind coagulation factors to their surface to form a stable fibrin clot). Such disorders may also create defects in platelet

aggregation and thromboxane A_2 and may produce abnormalities by preventing the release of adenosine diphosphate (defective platelet release reaction). The prognosis varies widely.

Causes and incidence

Abnormal platelet function disorders may be inherited (autosomal recessive) or acquired. Inherited disorders cause bone marrow production of platelets that are ineffective in the clotting mechanism. Acquired disorders result from the effects of such drugs as aspirin or carbenicillin; from such systemic diseases as uremia; or from other hematologic disorders.

Complication

- Hemorrhage

FACTS ABOUT PLATELET CONCENTRATE

Contents

- Platelets, white blood cells, some plasma
- Random platelets (ABO matched)
- Human leukocyte antigen (HLA) platelets (HLA-typed for multiple transfusions)

Amount

- 30 to 50 ml per donor
- 4 to 8 donor units given each time (each unit should raise the platelet count by 5,000/µl)

Shelf life

- 6 to 72 hours (best used within 24 hours)

Signs and symptoms

Generally, the sudden appearance of petechiae or purpura or excessive bruising and bleeding of the nose and gums are the first overt signs of

platelet function disorders. More serious signs are external hemorrhage, internal hemorrhage into the muscles and visceral organs, or excessive bleeding during surgery.

Diagnosis

Prolonged bleeding time in a patient with both a normal platelet count and normal clotting factors suggests this diagnosis. Determination of the defective mechanism requires a blood film and a platelet function test to measure platelet release reaction and aggregation. Depending on the type of platelet dysfunction, some or all of the test results may be abnormal.

Other typical laboratory findings are poor clot retraction and decreased prothrombin conversion. Baseline testing includes complete blood count and differential and appropriate tests to determine hemorrhage sites. In platelet function disorders, plasma clotting factors, platelet counts, prothrombin and partial thromboplastin levels, and thrombin times are usually normal.

Treatment

Platelet replacement is the only satisfactory treatment for inherited platelet dysfunction. However, acquired platelet function disorders respond to adequate treatment of the underlying disease or discontinuation of damaging drug therapy. Plasmapheresis effectively controls bleeding caused by a plasma element that's inhibiting platelet function. During this procedure, one or more units of whole blood are removed from the patient; the plasma is removed from the whole blood, and the remaining packed red blood cells are reinfused. (See *Facts about platelet concentrate*.)

Special considerations

- Obtain an accurate patient history, including onset of bleeding, use of drugs (especially aspirin), and family history of bleeding disorders.
- Watch closely for bleeding from skin, nose, gums, GI tract, or an injury site.

- Help the patient avoid unnecessary trauma. Advise him to tell his dentist about this condition before undergoing oral surgery. (Also stress the need for good oral hygiene to help prevent the need for such surgery.)
- Alert other care team members to the patient's hemorrhagic potential, especially before he undergoes diagnostic tests or surgery that may cause trauma and bleeding.
- Observe the patient undergoing plasmapheresis for hypovolemia, hypotension, tachycardia, and other signs of volume depletion.
- If platelet dysfunction is inherited, help the patient and his family understand and accept the disorder's nature. Teach them how to manage potential bleeding episodes. Warn them that petechiae, ecchymoses, and bleeding from the nose, gums, and GI tract signal abnormal bleeding and should be reported immediately.
- Tell the patient with a known coagulopathy or hepatic disease to avoid aspirin, aspirin compounds, and other agents that impair coagulation.
- Advise the patient to wear a medical identification bracelet or to carry a card identifying him as a potential bleeder.

Von Willebrand's disease

Von Willebrand's disease is a hereditary bleeding disorder characterized by prolonged bleeding time; moderate deficiency of von Willebrand factor (VWF), clotting factor VIII (antihemophilic factor) and, possibly, factor VIII coagulant protein (VIII:C); and impaired platelet function. This disease commonly causes bleeding from the skin or mucosal surfaces and, in females, excessive uterine bleeding. Bleeding may range from mild and asymptomatic to severe, potentially fatal hemorrhage. The prognosis, however, is usually good.

The three types of von Willebrand's disease are:

- *Type 1:* the most common form; there's decreased VWF and factor VIII may be below normal; this is the mildest form
- *Type 2:* the VWF contains a defect causing it to not function properly; there are four subtypes: 2A, 2B, 2M and 2N; it's important to know

which subtype as each is treated differently

- *Type 3:* this is the rarest and most severe form; there's no VWF and factor VIII is at low levels.

Causes and incidence

Unlike hemophilia, von Willebrand's disease is inherited as an autosomal dominant trait that affects males and females equally. One theory of pathophysiology holds that mild to moderate deficiency of factor VIII and defective platelet adhesion prolong coagulation time. Specifically, this results from a deficiency of the VWF, which stabilizes the factor VIII molecule and is needed for proper platelet function.

Defective platelet function is characterized by:

- decreased agglutination and adhesion at the bleeding site
- reduced platelet retention when filtered through a column of packed glass beads
- diminished ristocetin-induced platelet aggregation.

Recently, an acquired form has been identified in patients with cancer and immune disorders.

Von Willebrand's disease, which doesn't have any racial or ethnic associations, affects about 1% of the population.

Complication

- Severe, potentially life-threatening hemorrhage

Signs and symptoms

Von Willebrand's disease produces easy bruising, epistaxis, and bleeding from the gums. Petechiae are rarely seen. Severe forms of this disease may cause hemorrhage after laceration or surgery, menorrhagia, and GI bleeding. Excessive postpartum bleeding is uncommon because factor VIII levels and bleeding time abnormalities become less pronounced during pregnancy. Massive soft-tissue hemorrhage and bleeding into joints seldom occur. Severity of bleeding may lessen with age, and

bleeding episodes occur sporadically—a patient may bleed excessively after one dental extraction but not after another.

Diagnosis

Diagnosis is difficult because symptoms are mild, laboratory values are borderline, and factor VIII levels fluctuate. However, a positive family history and characteristic bleeding patterns and laboratory values help establish the diagnosis. Typical laboratory data include:

- prolonged bleeding time (more than 6 minutes)
- slightly prolonged partial thromboplastin time (more than 45 seconds)
- absent or reduced levels of factor VIII-related antigens and low factor VIII activity level
- defective in vitro platelet aggregation (using the ristocetin coagulation factor assay test)
- normal platelet count and normal clot retraction.

Treatment

The goals of treatment are to shorten bleeding time by local measures and to replace factor VIII (and, consequently, VWF) by infusion of cryoprecipitate or blood fractions that are rich in factor VIII.

During bleeding and before surgery, I.V. infusion of cryoprecipitate or fresh frozen

plasma (in quantities sufficient to raise factor VIII levels to 50% of normal) shortens bleeding time. Desmopressin given parenterally or intranasally is effective in raising serum levels of VWF.

Special considerations

The care plan should include local measures to control bleeding and patient teaching to prevent bleeding, unnecessary trauma, and complications.

- After surgery, monitor bleeding time for 24 to 48 hours, and watch for signs of new bleeding.

- During a bleeding episode, elevate and apply cold compresses and gentle pressure to the bleeding site.
- Refer parents of affected children for genetic counseling.
- Advise the patient to consult the physician after even minor trauma and before all surgery to determine if replacement of blood components is necessary.
- Instruct the patient to watch for signs of hepatitis within 6 weeks to 6 months after transfusion.
- Warn the patient against using aspirin and other drugs that impair platelet function.
- Advise the patient who has a severe form to avoid contact sports.

Disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) occurs as a life-threatening complication of diseases and conditions that accelerate clotting, causing small blood vessel occlusion, organ necrosis, depletion of circulating clotting factors and platelets, and activation of the fibrinolytic system. This, in turn, can provoke severe hemorrhage. (See *Three mechanisms of DIC*.) Clotting in the microcirculation usually affects the kidneys and extremities but may occur in the brain, lungs, pituitary and adrenal glands, and GI mucosa. Other conditions, such as vitamin K deficiency, hepatic disease, and anticoagulant therapy, may cause a similar hemorrhage. DIC, also called consumption coagulopathy or defibrination syndrome, is generally an acute condition but may be chronic in cancer patients. The prognosis depends on early detection and treatment, the hemorrhage's severity, and treatment of the underlying disease or condition.

Causes

DIC may result from:

- infection—gram-negative or grampositive septicemia; viral, fungal, or rickettsial infection; protozoal infection
- obstetric complications—abruptio placentae, amniotic fluid embolism, retained dead fetus, septic abortion, and eclampsia

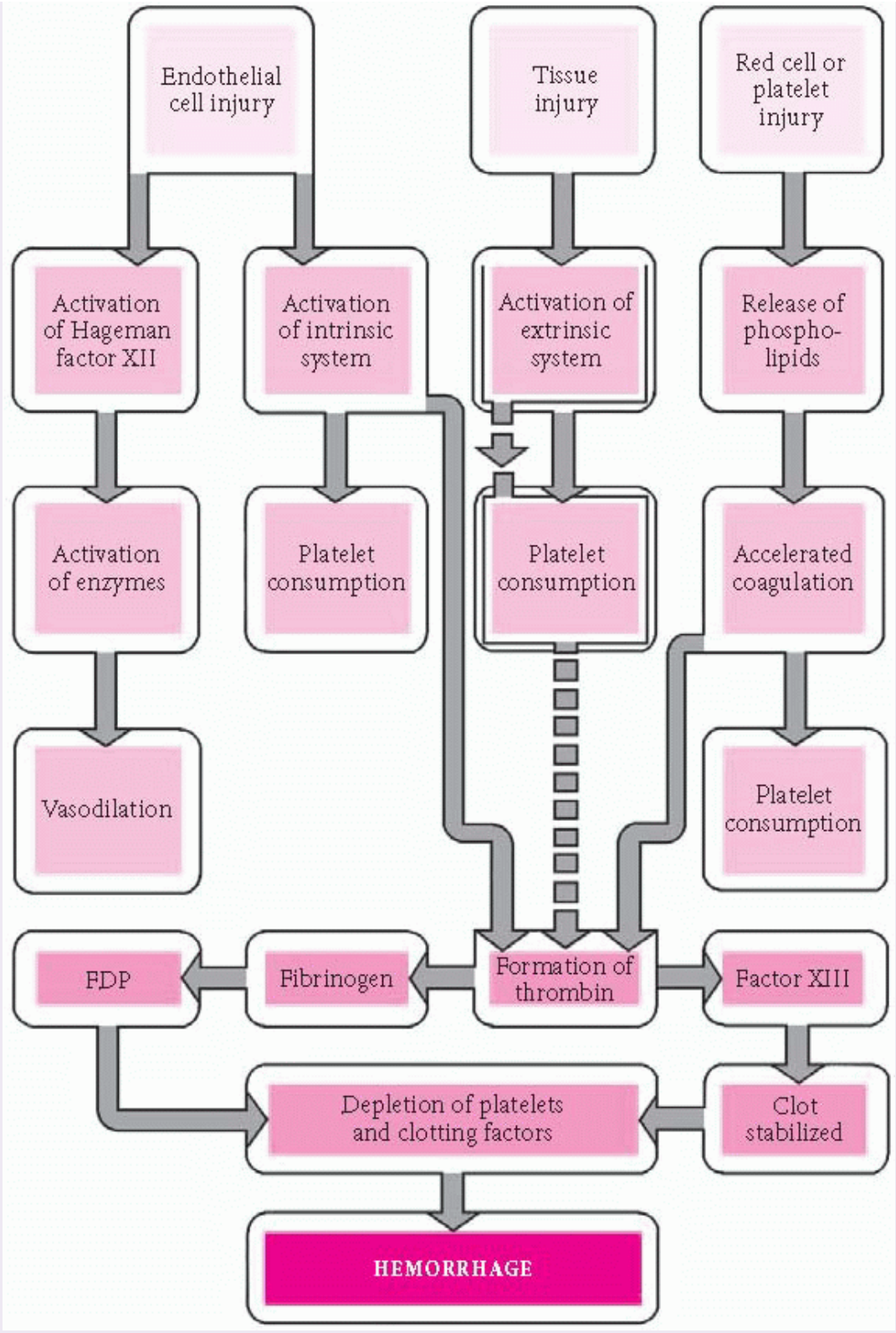
- neoplastic disease—acute leukemia, metastatic carcinoma, and aplastic anemia
- disorders that produce necrosis— extensive burns and trauma, brain tissue destruction, transplant rejection, and hepatic necrosis
- other factors—heatstroke, shock, poisonous snakebite, cirrhosis, fat embolism, incompatible blood transfusion, cardiac arrest, surgery necessitating cardiopulmonary bypass, giant hemangioma, severe venous thrombosis, and purpura fulminans.

It isn't clear why such disorders lead to DIC, nor is it certain that they lead to it through a common mechanism. In many patients, the triggering mechanisms may be the entrance of foreign protein into the circulation and vascular endothelial injury. Regardless of how DIC begins, the typical accelerated clotting results in generalized activation of prothrombin and a consequent excess of thrombin. Excess thrombin converts fibrinogen to fibrin, producing fibrin clots in the microcirculation. This process consumes exorbitant amounts of coagulation factors (especially fibrinogen, prothrombin, platelets, and factor V and factor VIII), causing hypofibrinogenemia, hypoprothrombinemia, thrombocytopenia, and deficiencies in factor V and factor VIII. Circulating thrombin activates the fibrinolytic system, which lyses fibrin clots into fibrin degradation products. The hemorrhage that occurs may be due largely to the anticoagulant activity of fibrin degradation products, as well as depletion of plasma coagulation factors.

PATHOPHYSIOLOGY

THREE MECHANISMS OF DIC

However disseminated intravascular coagulation (DIC) begins, accelerated clotting (characteristic of DIC) usually results in excess thrombin, which in turn causes fibrinolysis with excess fibrin formation and fibrin degradation products (FDP), activation of fibrin-stabilizing factor (factor XIII), consumption of platelet and clotting factors and, eventually, hemorrhage.


Endothelial cell injury
Tissue injury
Red cell or platelet injury
Activation of Hageman factor XII
Activation of intrinsic system
Activation of extrinsic system
Release of phospho-lipids
Activation of enzymes
Platelet consumption
Platelet consumption
Accelerated coagulation
Vasodilation
Platelet consumption
FDP
Fibrinogen
Formation of thrombin
Factor XIII
Depletion of platelets and clotting factors
Clot stabilized
HEMORRHAGE

Complications

- Ischemia of legs, arms, or organs
- Severe bleeding
- Stroke

Signs and symptoms

The most significant feature of DIC is abnormal bleeding, *without* a history of a serious hemorrhagic disorder. Principal signs of such bleeding include cutaneous oozing, petechiae, ecchymoses, and hematomas caused by bleeding into the skin. Bleeding from surgical or I.V. sites and from the GI tract are equally significant signs, as are acrocyanosis (cyanosis of the extremities) and signs of acute tubular necrosis. Related signs, symptoms, and other effects include nausea, vomiting, dyspnea, oliguria, seizures, coma, shock, major organ failure, confusion, epistaxis, hemoptysis, and severe muscle, back, abdominal, and chest pain.

Diagnosis

Abnormal bleeding in the absence of a known hematologic disorder suggests DIC but may be late in the pathophysiologic process. Initial laboratory findings reflect coagulation factor deficiencies.

- decreased platelet count: less than 100,000/µl
- decreased fibrinogen level: less than 150 mg/dl

As the excessive clot breaks down, hemorrhagic diathesis occurs, and test results reflect coagulation abnormalities:

- prolonged prothrombin time: more than 15 seconds
- prolonged partial thromboplastin time: more than 60 seconds
- increased fibrin degradation products: commonly more than 45 mcg/ml.

Other supportive data include positive fibrin monomers, diminished levels of factors V and VIII, fragmentation of red blood cells (RBCs), and

decreased hemoglobin (Hb) level (less than 10 g/dl). Assessment of renal status demonstrates reduction in urine output (less than 30 ml/hour) and elevated blood urea nitrogen (more than 25 mg/dl) and serum creatinine (more than 1.3 mg/dl) levels.

A positive D-dimer test (results less than 1:8 dilution and decreased levels of factors V and VIII) is specific for DIC. Confirming the diagnosis may be difficult because many of these test results also occur in other disorders (primary fibrinolysis, for example).

Treatment

Successful management of DIC necessitates prompt recognition and adequate treatment of the underlying disorder. Treatment may be supportive when the underlying disorder is self-limiting or highly specific. If the patient isn't bleeding, supportive care alone may reverse DIC. However, bleeding may require administration of blood, fresh frozen plasma, platelets, or packed RBCs to support hemostasis. Cryoprecipitates may also be used if fibrinogen is significantly decreased. Heparin is used in early stages to prevent microclotting and is sometimes used in combination with replacement therapy.

Special considerations

Patient care must focus on early recognition of abnormal bleeding, prompt treatment of the underlying disorders, and prevention of further bleeding.

- To avoid dislodging clots and causing fresh bleeding, don't scrub bleeding areas. Use pressure, cold compresses, and topical hemostatic agents to control bleeding.
- To prevent injury, enforce complete bed rest during bleeding episodes. If the patient is agitated, pad the side rails.
- Check all I.V. and venipuncture sites frequently for bleeding. Apply pressure to injection sites for at least 20 minutes. Alert other personnel to his tendency to hemorrhage.
- Monitor intake and output hourly in acute DIC, especially when administering blood products. Watch for transfusion reactions and signs of fluid overload. To measure the amount of blood lost, weigh

dressings and linen, and record drainage. Weigh the patient daily, particularly if there's renal involvement.

- Watch for bleeding from the GI and genitourinary tracts. If you suspect intra-abdominal bleeding, measure the patient's abdominal girth at least every 4 hours, and monitor closely for signs of shock.

- Monitor the results of serial blood studies (particularly hematocrit, Hb levels, and coagulation times).
- Explain all diagnostic tests and procedures. Allow time for questions.
- Inform the patient's family of his progress. Prepare them for his appearance (I.V. lines, nasogastric tubes, bruises, and dried blood). Provide emotional support for the patient and his family. As needed, enlist the aid of a social worker, chaplain, and other members of the health care team in providing such support.

MISCELLANEOUS DISORDERS

Granulocytopenia and lymphocytopenia

Granulocytopenia (also called *agranulocytosis*) is characterized by a marked reduction in the number of circulating granulocytes. Although this implies all the granulocytes (neutrophils, basophils, and eosinophils) are reduced, granulocytopenia usually refers to decreased neutrophils. (See *Understanding neutropenia,* page 538.) This disorder, which can occur at any age, is associated with infections and ulcerative lesions of the throat, GI tract, other mucous membranes, and skin. The severest form is known as *agranulocytosis*.

Lymphocytopenia (sometimes called *lymphopenia*), a rare disorder, is a deficiency of circulating lymphocytes (leukocytes produced mainly in lymph nodes).

In both granulocytopenia and lymphocytopenia, the total leukocyte count (white blood cell [WBC] count) may reach dangerously low levels, leaving the body unprotected against infection. The prognosis in both disorders depends on the underlying cause and whether it can be treated. Untreated, severe granulocytopenia can be fatal in 3 to 6 days.

Causes

Granulocytopenia may result from diminished production of granulocytes in bone marrow, increased peripheral destruction of granulocytes, or greater utilization of granulocytes. Diminished production of granulocytes in bone marrow generally stems from radiation or drug therapy; it's a common adverse effect of antimetabolites and alkylating agents and may occur in the patient who is hypersensitive to phenothiazine, sulfonamides (and some sulfonamide derivatives), antibiotics, and antiarrhythmic drugs. Drug-induced granulocytopenia usually develops slowly and typically correlates with the dosage and duration of therapy. Production of granulocytes also decreases in conditions such as aplastic anemia and bone marrow malignancies and in some hereditary disorders (infantile genetic agranulocytosis).

The growing loss of peripheral granulocytes is due to increased splenic sequestration, diseases that destroy peripheral blood cells (viral and bacterial infections), and drugs that act as haptens (carrying antigens that attack blood cells and causing acute idiosyncratic or non-dose-related drug reactions). Infections such as infectious mononucleosis may result in granulocytopenia because of increased utilization of granulocytes.

Similarly, lymphocytopenia may result from decreased production, increased destruction, or loss of lymphocytes. Decreased production of lymphocytes may be secondary to a genetic or a thymic abnormality or to immunodeficiency disorders, such as thymic dysplasia or ataxiatelangiectasia. Increased destruction of lymphocytes may be secondary to radiation, chemotherapy, or human immunodeficiency virus infection. Loss of lymphocytes may follow postsurgical thoracic duct drainage, intestinal lymphangiectasia, or impaired intestinal lymphatic drainage (as in Whipple's disease).

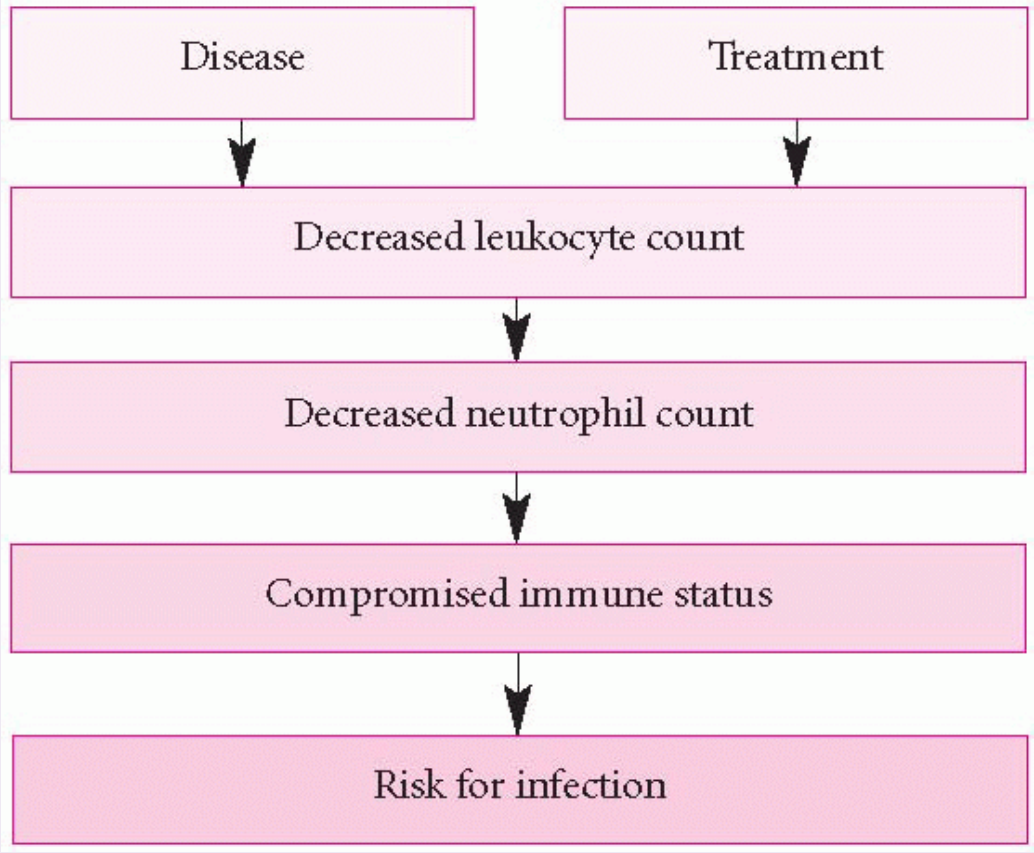
Lymphocyte depletion can also result from elevated plasma corticoid levels (due to stress, corticotropin or steroid treatment, or heart failure). Other disorders associated with lymphocyte depletion include Hodgkin's disease, leukemia, aplastic anemia, sarcoidosis, myasthenia gravis, lupus erythematosus, protein-calorie malnutrition, renal failure, terminal cancer, tuberculosis

and, in infants, severe combined immunodeficiency disease (SCID).

PATHOPHYSIOLOGY

UNDERSTANDING NEUTROPENIA

Neutropenia, a deficiency in the number of mature neutrophils, is the most common immune system deficiency. It can result from a disease or from radiation or drug therapy. Common infections that occur secondary to neutropenia include aerobic gram-negative bacilli and *Staphylococcus aureus* and certain fungal infections, such as candidiasis and aspergillosis.



Complication

- Infection

Signs and symptoms

Characteristically, patients with granulocytopenia experience slowly progressive fatigue and weakness; however, if they develop an infection, they can exhibit sudden onset of fever and chills and mental status changes. Overt signs of infection (pus formation) are usually absent. Localized infection can quickly become systemic (bacteremic) or spread throughout an organ (pneumonia). All patients should be meticulously evaluated for even subtle signs of infection because untreated infections can lead to septic shock in 8 to 24 hours. If granulocytopenia results from an idiosyncratic drug reaction, signs of infection develop abruptly, without slowly progressive fatigue and weakness.

Patients with lymphocytopenia may exhibit enlarged lymph nodes, spleen, and tonsils and signs of an associated disease.

Diagnosis

Diagnosis of granulocytopenia necessitates a thorough patient history to check for precipitating factors. Physical examination for clinical effects of underlying disorders is also essential.

CONFIRMING DIAGNOSIS

A markedly decreased neutrophil count (less than 500/µl leads to severe bacterial infections) and a WBC count lower than 2,000/µl, with few observable granulocytes on complete blood count (CBC), confirm granulocytopenia.

Bone marrow examination shows a scarcity of granulocytic precursor cells beyond the most immature forms, but this may vary, depending on the cause.

A lymphocyte count below 1,500/µl in adults or below 3,000/µl in children indicates lymphocytopenia. Identifying the cause by evaluation of clinical status, bone marrow and lymph node biopsies, or other appropriate diagnostic tests helps establish the diagnosis.

Treatment

Effective management of granulocytopenia must identify and eliminate the cause and

control infection until the bone marrow can generate more leukocytes. In many cases, this means drug or radiation therapy must be stopped and antibiotic treatment begun immediately, even while awaiting test results. Treatment may also include an-tifungal preparations. Administration of granulocyte colony-stimulating factor (CSF) or granulocyte-macrophage CSF is a newer treatment used to stimulate bone marrow production of neutrophils. Spontaneous restoration of leukocyte production in bone marrow generally occurs within 1 to 3 weeks.

Treatment of lymphocytopenia includes eliminating the cause and managing any underlying disorders. For infants with SCID, therapy may include bone marrow transplantation.

Special considerations

- Monitor vital signs frequently. Obtain cultures from blood, throat, urine, mouth, nose, rectum, vagina, and sputum, as ordered. Give antibiotics as scheduled.
- Explain the necessity of infection protection procedures to the patient and his family. Teach proper hand-washing technique and the correct use of gowns and masks. Prevent patient contact with staff or visitors with respiratory infections.
- Maintain adequate nutrition and hydration because malnutrition aggravates immunosuppression. Make sure the patient with mouth ulcerations receives a high-calorie liquid diet. Offer a straw to make drinking less painful.
- Provide warm saline water gargles and rinses, analgesics, and anesthetic lozenges. Good oral hygiene promotes comfort and facilitates healing.
- Ensure adequate rest, which is essential to the mobilization of the body's defenses against infection. Provide good skin and perineal care.
- Monitor CBC and differential, blood culture results, serum electrolyte levels, intake and output, and daily weight.

- To help detect granulocytopenia and lymphocytopenia in the early, most treatable stages, monitor the WBC count of any patient receiving radiation or chemotherapy. After the patient has developed bone marrow depression, he must zealously avoid exposure to infection.
- Advise the patient with known or suspected sensitivity to a drug that may lead to granulocytopenia or lymphocytopenia to alert medical personnel to this sensitivity in the future.

Hypersplenism

Hypersplenism is a syndrome marked by exaggerated splenic activity and, possibly, splenomegaly. This disorder results in peripheral blood cell deficiency as the spleen traps and destroys peripheral blood cells.

Causes

Hypersplenism may be idiopathic (primary) or secondary to an extrasplenic disorder, such as chronic malaria, polycythemia vera, or rheumatoid arthritis. (See *Causes of splenomegaly,* page 540.) In hypersplenism, the spleen's normal filtering and phagocytic functions accelerate indiscriminately, automatically removing antibody-coated, aging, and abnormal cells, even though some cells may be functionally normal. The spleen may also temporarily sequester normal platelets and red blood cells (RBCs), withholding them from circulation. In this manner, the enlarged spleen may trap as much as 90% of the body's platelets and up to 45% of its RBC mass.

Signs and symptoms

Most patients with hypersplenism develop anemia, leukopenia, or thrombocytopenia, in many cases with splenomegaly. They may contract bacterial infections frequently, bruise easily, hemorrhage spontaneously from the mucous membranes and GI or genitourinary tract, and suffer ulcerations of the mouth, legs, and feet. They commonly develop fever, weakness, and palpitations. Patients with secondary hypersplenism may have other clinical abnormalities, depending on the underlying disease.

CAUSES OF SPLENOMEGALY

Infectious

- Acute (abscesses, subacute infective endocarditis), chronic (tuberculosis, malaria, Felty's syndrome)

Congestive

- Cirrhosis, thrombosis

Hyperplastic

- Hemolytic anemia, polycythemia vera

Infiltrative

- Gaucher's disease, Niemann-Pick disease

Cystic or neoplastic

- Cysts, leukemia, lymphoma, myelofibrosis

Diagnosis

Diagnosis requires evidence of abnormal splenic destruction or sequestration of RBCs or platelets and splenomegaly.

CONFIRMING DIAGNOSIS

The most definitive test measures erythrocytes in the spleen and liver after I.V. infusion of chromium-labeled RBCs or platelets. A high spleen-liver ratio of radioactivity indicates splenic destruction or sequestration.

Complete blood count shows decreased hemoglobin level (as low as 4 g/dl), white blood cell count (less than 4,000/mcl), and platelet count (less than 125,000/mcl) and an elevated reticulocyte count (more than 75,000/mcl). Splenic biopsy, scan, and angiography may be useful; biopsy is hazardous and should be avoided if possible. In sequestration, the spleen is palpable. Use abdominal palpation cautiously because it may create injury, bleeding, or rupture.

Treatment

Splenectomy is indicated only in transfusion-dependent patients who are refractory to medical therapy. Splenectomy seldom cures the patient, but it does correct the effects of cytopenia. Postoperative complications may include infection and thromboembolic disease. Occasionally, splenectomy may result in accelerated blood cell destruction in the bone marrow and liver. Secondary hypersplenism necessitates treatment of the underlying disease.

Special considerations

- If splenectomy is scheduled, administer preoperative transfusions of blood or blood products (fresh frozen plasma and platelets) to replace deficient blood elements. Also treat symptoms or complications of any underlying disorder.
- Postoperatively, monitor vital signs. Check for any excessive drainage or apparent bleeding. Watch for infection, thromboembolism, and abdominal distention. Keep the nasogastric tube patent; listen for bowel sounds. Instruct the patient to perform deep-breathing exercises, and encourage early ambulation to prevent respiratory complications and venous stasis.

ELDER TIP

Older adults may be at higher risk for infection because of decreased leukocyte and lymphocyte production. Fewer and weaker lymphocytes and immune system changes diminish the antigen-antibody response in older adults.

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