KHARKIV NATIONAL MEDICAL UNIVERSITY
DEPARTMENT OF INTERNAL MEDICINE N3

METHODOLOGICAL RECOMMENDATIONS FOR STUDENTS

"Anemias"

Kharkiv 2012

Module 4. "The basic foundations of diagnostics, treatment and prophylaxis of common hematological diseases".

Practical lesson N 26

"**Anemias (iron deficiency anemia, vitamin B_{12} deficiency anemia, folate deficiency anemia, aplastic anemia**"

Topicality

Globally, 50% of anemia is attributable to iron deficiency and accounts for around 841,000 deaths annually worldwide. Africa and parts of Asia bear 71% of the global mortality burden; North America represents only 1.4% of the total morbidity and mortality associated with iron deficiency.

Hemoglobinopathies are especially common in areas in which malaria is endemic. This clustering of hemoglobinopathies is assumed to reflect a selective survival advantage for the abnormal RBC, which presumably provide a less hospitable environment during the obligate RBC stages of the parasitic life cycle. Very young children with α-thalassemia are *more* susceptible to infection with the nonlethal *Plasmodium vivax*. Thalassemia might then favor a natural protection against infection with the more lethal *P. falciparum*.

Thalassemias are the most common genetic disorders in the world, affecting nearly 200 million people worldwide. About 15% of American blacks are silent carriers for α-thalassemia; α-thalassemia trait (minor) occurs in 3% of American blacks and in 1–15% of persons of Mediterranean origin. β-Thalassemia has a 10–15% incidence in individuals from the Mediterranean and Southeast Asia and 0.8% in American blacks. Sickle cell disease is the most common structural hemoglobinopathy occurring in heterozygous form in ~8% of American blacks and in homozygous form in 1 in 400. Between 2 and 3% of American blacks carry a hemoglobin C allele.

Learning Objectives:

- Define syndrome, anemia and certain forms of anemia (iron, B12-deficiency, folic acid deficiency, hemolytic, hypoplastic, hemorrhagic);
- To view the etiology and pathogenesis of different clinical forms of the disease;
- To view the modern classification of anemia;
- Learn to recognize the main symptoms and syndromes of anemia;
- To view the research methods that are used to diagnose anemia, indications and contraindications for their implementation, methods of implementation, the diagnostic value of each of them;
- Learn how to interpret the results of their own research;
- Learn to recognize certain types of anemia;
- Learn to prescribe treatment for anemia.

What should a student know?

 The main etiological factors and pathogenetical mechanisms of anemia;
 The main clinical symptoms of anemia;
 Methods of physical examination of patients with the disease;
 Diagnostic value of hematocrit, blood count and myelogram;
 Diagnostic value of the results of determination of ferritin, iron, vitamin B12, folic acid;
 Identification of iron-binding properties of blood;
 Desferal test and methodology for clinical evaluation of results;
 Coombs test, and the methodology for clinical evaluation of the results;
 Test of Ham, technique and clinical evaluation of the results;
 Diagnostic value of sternal puncture for anemia, indications, contraindications;
 List of additional instrumental studies, which are used to determine the source of blood loss and for the differential diagnosis;
 The complications of the disease;
 Features of patients with anemia;
 Features of treatment of anemia (lifestyle modification, nutritional therapy, drug therapy, transfusion therapy);
 Preventive measures to prevent the development of anemia.

What should a student know?

 The main clinical syndromes with anemia;
 To identify the program of examination of patients with the disease;
 To interpret the results of laboratory tests;
 To conduct differential diagnostics of diseases that are accompanied by anemia syndrome;
 To prescribe antianemic medications;
 To assess the prognosis of patients with anemia.

The list of practical skills that students should learn:

o Inspection of the skin, skin derivatives, the visible mucous membranes;
o Palpation of the pulse;
o Identification of blood pressure;
o Palpation of the precordial region;
o Determination of a relative and absolute dullness of the heart;
o Auscultation of the heart;
o Inspection of the abdomen;
o Superficial palpation of the abdomen;
o Deep methodical sliding palpation of the abdomen;
o percussion and palpation of the liver and spleen.

Definition

Anemia It is the clinical hematological syndrome, which is characterized by decreased level of hemoglobin and erythrocytes in blood and reduced O_2 delivery to tissue .

Anemia is present in case of hemoglobin level less than 130 g/L and erythrocytes count less than $4x10^{12}$/L in males and, accordingly less than 120 g/L and 3,5 $x10^{12}$ /L in females.

Erythropoiesis is a controlled physiologic process. In response to changes in tissue oxygen availability, the kidney regulates production and release of erythropoietin that stimulates the bone marrow to produce and release red blood cells. Erythrocytes originate from pluripotent stem cells in the bone marrow and undergo multiple steps of differentiation and maturation. Early stages of red cell production consist of large cells with immature nuclei (pronormoblasts and basophilic normoblasts). As cells mature, Hb is incorporated, the nucleus is extruded, and cell size decreases. Various nutrients are needed for normal erythropoiesis. Lack of B_{12} or folate can interfere with cell maturation, resulting in the release of megaloblasts (erythroid precursors with immature nuclei). Iron deficiency interferes with Hb production and incorporation into the maturing cells, which continue to divide, resulting in the release of smaller cells (microcytosis).

Pathophysiology

Anemia, which has many causes, is not a single disease entity but a sign of disease. Regardless of the cause, anemia is associated with a reduction in circulating Hb because of reduced numbers of erythrocytes or less Hb per erythrocyte.

The number of erythrocytes in normal people varies with age, sex, and atmospheric pressure. People who live at high altitudes have more erythrocytes to compensate for the reduced oxygen in the air. At sea level, the average man has 5.5×10^{12} erythrocytes/L (5.5×10^6/mm^3). The erythrocytes occupy approximately 47% of the blood and are often referred to as the packed cell volume or hematocrit (Hct). Blood from healthy men contains approximately 9.9 mmol/L (16 g/dL) Hb. All these parameters are lower for healthy women. Values for neonates, which show no sex differences, are higher at birth, but after several weeks they decrease to below those of women. The physiologic result of low circulating Hb is the reduced capacity for blood to carry oxygen. Consequently, less oxygen is available to tissues, including those of the heart, brain, and muscles, leading to the clinical manifestations of anemia.

Clinical Presentation and Diagnosis

Regardless of the cause of anemia, the clinical features depend on the rate of development and the compensatory ability of the cardiovascular and pulmonary system to adjust to tissue hypoxia. Lower Hb levels often are tolerated with minimal symptoms if the anemia develops slowly and the body is able to compensate.

Signs and Symptoms

Overt signs of anemia are : fatigue, pallor, dyspnea, light-headedness, dizziness, palpitations, increased heart rate, chest pain, loss of concentration.

Cardiomegaly and high-output heart failure also are possible in severe cases. Although the symptoms of anemia are distinctive, they can also be manifestations of other disorders, such as cancer or an inflammatory process. A comprehensive history and physical examination are important in the assessment of the anemic patient. More specifically, dietary habits, drug histories, surgical procedures, and occupation should be documented. Careful questioning about blood loss, menses, gastrointestinal symptoms, and history of pregnancy may provide useful information.

Diagnosis

A detailed medical and medication history along with hematologic and biochemical tests, including a full blood screen, are essential for identifying the type of anemia and in many cases directing the treatment. As the nutritional anemias progress in stages (normal, negative nutrient balance, nutrient depletion, nutrient deficiency, anemia), monitoring early indicators of depletion may prevent the progression to overt anemia. Risk factors for certain vitamin deficiencies and reported symptoms often suggest the possible cause of anemia or alert the physician to the potential for anemia.

Hematologic Tests

Hematologic tests are less expensive and more available than biochemical tests and provide information on the characteristics of the red blood cells. A full blood screen provides information on Hb and Hct levels as well as cell size and color. Many aspects of the cellular elements of blood can be quantified by automated blood analyzers, including blood Hb concentration, cell counts, and the mean corpuscular volume (MCV). From these primary measurements, the Hct, mean corpuscular hemoglobin (MCH), and the mean corpuscular hemoglobin concentration (MCHC) are calculated automatically. MCV, MCH, and MCHC are collectively known as the erythrocyte indices. The MCV correlates with cell size (smaller cells take up less volume) and is particularly valuable in differentiating microcytic anemias, which have a reduced MCV (<80 fL), from macrocytic anemias, which have a greater than normal MCV (>100 fL). However, the MCV may appear normal in mixed anemias, where the microcytic cells of iron deficiency are counterbalanced by the macrocytic cells of B_{12} or folate deficiency. In this instance, a peripheral blood smear can aid in identifying the existence of a mixed anemia. The MCH and MCHC provide information on cell color [lower Hb, less color (hypochromia)]. Hypochromic anemias, such as iron deficiency anemia, have a low MCHC indicating lower-than-normal Hb concentrations. Another parameter, the red blood cell distribution width (RDW), is an index of the variation in cell volume of the erythrocyte population. With iron deficiency anemia, there is an increased RDW, reflecting the anisocytosis (cells of unequal size) seen in blood smears.

Other hematologic investigations include reticulocyte counts, differential white cell count, platelet count, and microscopic examination of peripheral blood smears and bone marrow aspirates. The normal life span of an erythrocyte is 120 days. As old erythrocytes are removed from the circulation by the reticuloendothelial system, they are replaced by young erythrocytes from the bone marrow. These immature cells, called reticulocytes, make up 1% to 1.5% of the total erythrocyte population in a normal person. Because reticulocytes are a young population of red blood cells, they are an important marker of bone marrow activity. Reticulocytosis, an increase in reticulocyte numbers, indicates increased bone marrow activity. Transient reticulocytosis often occurs in response to iron, B_{12}, or folic acid therapy for the respective deficiency states.

Biochemical Tests

Biochemical tests for assessing anemias include measurement of serum iron vitamin concentrations (B_{12}, folate), transport proteins (transferrin, transcobalamin II [TCII]), saturation of protein- binding sites (transferrin saturation), and storage amounts (ferritin).

In general, the diagnosis of a nutritional anemia depends on an accurate and complete medical, drug, and symptom history and assessment of multiple laboratory and biochemical tests rather than a single result.

Table 1

Selected Hematologic and Biochemical Parameters

Component	Specimen	Sex	Conventional units	SI units
Hematocrit	blood	male	45%–52%	0.45–0.52
		female	37%–48%	0.37–0.48
Hemoglobin	blood	male	13%–18% g/dL	130–180 g/L
		female	12%–16% g/dL	120–160 g/L
Erythrocyte count	blood	Both	4.2%–5.9% × 10^6/mm	4.2–5.9 × 10^6/mm
Reticulocyte count	blood	Both	0.5%–1.5% erythrocytes	0.5%–1.5% erythrocytes
Mean corpuscular volume	erythrocytes	Both		80–94 fmol
Mean corpuscular hemoglobin	erythrocytes	Both	27–32 pg	1.7–2.0 fmol
Mean corpuscular hemoglobin concentration	erythrocytes	Both	32–36 g/dL	19–22.8 mmol/L
Red cell distribution width	erythrocytes	Both	11.5%–14.5%	
Iron	serum	Male	80–200 μg/dL	14–35 μmol/L
		Female	60–190 μg/dL	11–29 μmol/L
Transferrin	Serum	Both	170-370 mg/dL	1.7–3.7 g/L
Ferritin	Serum	Both	1.5–30 μg/dL	15–300 μg/L

Iron Deficiency Anemia

Iron deficiency occurs when the body's iron stores are insufficient for the normal formation of Hb, iron-containing enzymes, and other functional iron compounds such as myoglobin and those of the cytochrome system. Iron deficiency can be classified according to its severity: normal stores; negative iron balance; iron store depletion (low serum ferritin); decreased serum iron [low serum iron, increased total iron-binding capacity (TIBC)]; and anemia (reduced Hb with microcytic, hypochromic erythrocytes).3 Erythrocytes of patients with mild, early-stage iron deficiency often appear to be normal in color and size (i.e., normochromic, normocytic).

Physiologic Importance of Iron

Iron is an essential element for many physiologic processes, including erythropoiesis, tissue respiration, and several enzyme-catalyzed reactions.1 The average adult body contains 3 to 5 g elemental iron, distributed into two major components: functional iron and storage.1,3 Functional iron exists predominantly as Hb (1.5–3 g) in circulating erythrocytes, with lesser amounts in iron containing proteins such as myoglobin and cytochromes (0.4 g), 3 to 7 mg bound to transferrin in plasma, and the remainder in storage iron in the form of ferritin or hemosiderin.

Hb is the oxygen-binding protein in erythrocytes that transports oxygen absorbed from the lungs to the tissues. Each Hb molecule consists of a globin surrounded by four heme groups that contain all the iron. Globin consists of linked pairs of polypeptide chains. Fetal Hb has two α- and two γ-globin chains. In normal erythrocyte development, the γ-chains are replaced by β-chains, and a normal human adult has two α- and two β-chains. The composition of these chains differs in patients with genetically determined disorders such as thalassemia and sickle cell anemia.

Hb forms an unstable, reversible bond with oxygen, allowing oxygen release at a lower oxygen tension that is encountered in the tissues. In iron deficiency anemia and other chronic anemias, Hb has a reduced affinity for oxygen. This allows oxygen to transfer more readily from the erythrocytes to the tissues. Myoglobin, a hemoprotein in muscle, accepts oxygen from Hb and acts as an oxygen store in muscle. If oxygen supply is limited, myoglobin releases its oxygen to cytochrome oxidase, the terminal enzyme in the mitochondrial respiratory chain, which has a higher affinity for oxygen than myoglobin, allowing oxidative phosphorylation to occur.

Transferrin, a β-globulin synthesized by the liver, is a specific iron-binding protein in blood that transports iron through the plasma and extravascular space. Each molecule of transferrin can bind two molecules of iron in the ferric state (Fe^{3+}). In normal circumstances, it is only about 30% to 50% saturated. The ability of transferrin to bind iron is called the iron-binding capacity. The total iron binding capacity (TIBC), which reflects serum transferrin concentrations, is a well-recognized value in the investigation of anemias. It represents the amount of iron that can bind to transferrin to give 100% saturation of the binding sites. The TIBC

is high in iron deficiency and low in iron overload. Most cells obtain their iron from transferrin. In the case of reticulocytes and developing erythrocytes in the bone marrow, most of the iron taken up is used for Hb synthesis.

Storage iron (0.3–1.5 g), in the form of ferritin and hemosiderin, is located mainly in the parenchymal cells of the liver, the reticuloendothelial cells of the spleen, and bone marrow, and it replenishes functional iron. Iron stores account for one third of body iron in healthy men. Iron stores are more variable and are generally lower in children and women of childbearing potential. Low iron stores are an early sign of iron deficiency and may help differentiate between iron deficiency anemia and other causes of anemia.

Iron Needs

Body iron usually is kept constant by a delicate balance between the amount lost and absorbed. There is no physiologic mechanism for excreting iron in humans. Consequently, there is only a limited ability to compensate for excessive loss or absorption of iron. Iron balance is a conservative system, and in the normal adult, even if iron intake is negligible, it takes at least 2 to 3 years to develop iron deficiency.

Iron needs are determined by total losses from the body. Daily iron needs vary according to age and sex. Total daily iron loss amounts to 1 mg daily in men. Iron losses in women of childbearing potential are higher than those in men because of menstruation and pregnancy. Iron is lost from the gastrointestinal tract by sloughing of iron-containing mucosal cells and extravasation of erythrocytes, by skin exfoliation, and by shedding of urinary tract epithelial cells. Iron loss through sweat is minimal.

Blood loss in menstruating women varies, but if it exceeds 80 mL, it can lead to iron deficiency. Average iron losses through menstruation are about 0.3 to 0.5 mg daily. Menstrual iron losses are lower in women taking oral contraceptives and higher in those using an intrauterine device.

Iron needs increase to 3 to 4 mg daily during pregnancy to account for obligatory losses, the expanded maternal erythrocyte mass that occurs in pregnancy and in the placenta and fetus. Iron needs are greatest in the second and third trimester when the highest fetal erythrocyte needs occur. Some of the iron incorporated in the expanded maternal erythrocyte mass returns to the iron pool after pregnancy, but peripartum blood loss partly nullifies this contribution. Because menstruation does not start until several weeks after delivery, iron losses are reduced. However, breast-feeding offsets some of the gain.

The need for iron is high in the first year of life and throughout childhood because of rapid growth and erythropoiesis during this period. Normal full-term infants need to absorb a minimum of 0.3 mg of iron daily in the first year of life. Premature infants can need up to 1 mg daily. Children's iron needs increase with age.

Iron Absorption

Iron absorption is regulated by iron needs and body stores. When iron stores are low or depleted, a higher proportion of available iron is absorbed. Absorption decreases when the stores are replete. The serum ferritin concentration, which reflects body iron stores, is inversely related to iron absorption. However, this feedback process can be overwhelmed when large amounts of iron are presented for absorption (e.g., in iron overdose or toxicity cases). In some clinical states, such as primary hemochromatosis, thalassemia, and sideroblastic anemia, iron absorption remains normal and even elevated despite increased iron stores.

The iron content of food and its bioavailability determine if the diet can meet physiologic needs. Dietary iron is present as two major pools: heme iron and nonheme iron. Heme iron, found only in meats, is two to three times more absorbable than nonheme iron, found in plant-based and iron- fortified foods. Ingested heme compounds and organic nonheme iron complexes are broken down in the acid environment of the stomach to ferric ions (Fe^{3+}) and heme molecules, respectively. The stomach's acidity promotes reduction of iron from the ferric state to the ferrous state (Fe^{2+}), which is better absorbed. Patients with achlorhydria secondary to age or gastrectomy tend to absorb nonheme iron poorly.

Iron is absorbed primarily in the upper duodenum. The iron-absorptive capacity is limited by the rate at which iron is transferred from the intestinal lumen to the plasma. The reduced (ferrous) iron binds to specific sites on the lumen and is actively carried across the intestinal membrane. Iron absorbed by these cells is incorporated into an iron carrier pool, most of which is deposited as ferritin or used by the mitochondria for enzyme synthesis. A small amount of iron is lost through the normal sloughing of the mucosal cells in the gastrointestinal tract. A smaller proportion of the iron from the carrier pool is transferred to the plasma, where the ferric form binds tightly to transferrin.

A number of factors can inhibit or promote iron absorption. Foods that can reduce iron absorption by forming less soluble complexes include coffee, tea, milk and milk products, eggs, whole grain breads and cereals, and any food containing bicarbonates, carbonates, oxalates, or phosphates. Commercial processing or enhancers can improve absorption from food in some cases. Enhancers of nonheme iron absorption are food acids such as citric, lactic, or ascorbic acids, and meats. Ascorbic acid, the most powerful promoter, has a dose-related effect on nonheme iron absorption. In its presence, ferric iron is converted to the ferrous state, maintaining iron solubility in the alkaline environment of the duodenum and upper jejunum. Ascorbic acid also forms an alkaline-stable chelate with ferric chloride in the stomach. Meat, itself a rich source of iron, also promotes absorption of nonheme iron. Approximately 1 g of meat enhances nonheme iron absorption to about the same extent as 1 mg of ascorbic acid. Citric acid, a common food additive and a less powerful promoter of iron absorption, has an additive effect to ascorbic acid.

Epidemiology

Occurrence

Iron deficiency, estimated to occur in more than 2.5 billion people throughout the world, is the most common cause of nutritional anemia.

Etiology

The primary causes of iron deficiency are listed in **Table 2**. Blood loss is the major cause of iron deficiency in men and nonmenstruating women and girls. Bleeding may be overt or occult. A common site of blood loss is the gastrointestinal tract. If bleeding is not obvious, a test for occult blood in the stool may give the first indication of blood loss. Common sources of blood loss in the gastrointestinal tract are peptic ulcers, esophageal varices, and colon cancer. Nonsteroidal anti-inflammatory agents, such as aspirin and indomethacin, can cause gastrointestinal bleeding, especially if taken with warfarin. In the absence of upper gastrointestinal symptoms, investigations should be directed to the lower gastrointestinal tract. Bleeding hemorrhoids rarely result in anemia, but neoplasms are a common cause of bleeding, particularly in older adults. The incidence of colon cancer, which can cause bleeding, increases 40-fold between ages 40 and 80. Other causes of gastrointestinal blood loss include hookworm infestation, Meckel's diverticulum, and ulcerative colitis. Hookworm is a major cause of iron deficiency anemia in tropical areas.

Iron deficiency has also been noted in athletes, particularly adolescent girls, marathon runners, and other endurance athletes. Up to 50% of adolescent female athletes demonstrate some degree of iron depletion, but anemia is uncommon. Blood loss is believed to result from ischemia of the gastrointestinal tract because blood is shunted to muscles during prolonged exercise. Marathon runners can lose at least 3 mg of iron daily for several days after a marathon race. Another short-term anemia related to sports is the dilutional anemia that can result from plasma volume expansion in the early weeks of conditioning.

Poor nutrition, defective intake, and decreased assimilation of iron rarely cause iron deficiency in people living in Western countries. Iron deficiency caused by inadequate dietary iron intake is predominantly a problem of infants, children, and pregnant women, whose daily needs are higher. In some populations, where the diet is mainly of vegetable origin with little meat, women are more likely to suffer from nutritional iron deficiency. Iron malabsorption may occasionally cause iron deficiency, although it is rarely an important cause unless iron stores are low or there are other contributing factors such as blood loss, pregnancy, or poor nutrition. The two most common conditions in which iron absorption is a problem are gluten enteropathy (celiac disease) and gastrectomy. Other conditions associated with iron deficiency anemia include pernicious anemia, pica syndrome, and chronic inflammatory disease such as rheumatoid arthritis.

Table 2

Factors Associated With Iron Deficiency

Factor	Association
Dietary	Starvation, poverty, vegetarianism, religious practice, food fads
Blood loss (women and girls)	Menstruation, postmenopausal bleeding, pregnancy
Blood loss (general)	Esophageal varices, peptic ulcer, drug-induced gastritis, carcinomas of stomach and colon, ulcerative colitis, hemorrhoids, renal or bladder lesions (hematuria), hookworm infestation, other organ bleeding (hemoptysis), frequent blood donation, athletic training, widespread bleeding disorder
Malabsorption	Celiac disease (gluten-induced enteropathy), partial and total gastrectomy, chronic inflammation
Increased requirements	Rapid growth (as in childhood and adolescence), pregnancy; erythropoiesis

Clinical Presentation and Diagnosis

Signs and Symptoms

Iron deficiency precedes the manifestations of anemia. Most people with iron deficiency have minimal anemia and are asymptomatic. Progression to iron deficiency anemia is often insidious, although mildly lowered Hb concentrations generally decrease work capacity. The development of symptoms depends on the rate of iron loss and the body's ability to compensate. Symptoms generally become evident when the blood Hb concentration falls 100 g/L, although some patients remain asymptomatic even with Hb concentrations of 70 g/L).

The usual signs and symptoms of iron deficiency anemia are often present:

Cardiovascular syndrome:

- palpitations, angina, breathlessness;
- pallor, tachycardia, hypotension, systolic flow murmur, cardiac failure.

Asthenic syndrome:

- fatigue, headaches, faintness, sleepiness.

Digestive system injury:

- decreased appetite, belching, constipations, atrophic hypoacidic gastritis

Other problems caused by the gross epithelial changes associated with chronic iron deficiency (sideropenic syndrome) include brittle or spoon-shaped nails, angular stomatitis, atrophic tongue, pharyngeal and esophageal webs causing dysphagia, and atrophic gastric mucosa. Iron deficiency, in addition to its hematologic effects, may also be associated with diverse problems such as impaired work performance.

A common symptom of iron deficiency anemia is pica, a condition in which the person craves unusual substances that generally have no nutritional value, such as clay (geophagia), paper products, or starch (amylophagia). Pagophagia (pica for ice), or habitual ice eating, is a common form of pica in some communities. Other

people consume earth and particles of clay cooking pots. Such ingestions have led to metabolic problems, including heavy metal poisoning.

Diagnosis

Most cases of iron deficiency anemia are identified on the basis of a medical history, complete blood count, and peripheral smears. In iron deficiency anemia, hematologic changes are evident only after all body iron stores have been depleted and there is insufficient iron to maintain normal erythrocyte morphology and mass. Blood Hb concentrations and erythrocyte numbers are normal in mild cases. Serum ferritin is the first parameter to change with iron deficiency. As the deficiency worsens, the MCV and erythrocyte count decrease markedly, the RDW increases, and eventually, the Hb decreases. When Hb concentrations are 70 g/L or less for women 90 g/L or less for men, microscopic examination of peripheral blood smears shows hypochromia and poikilocytosis.

Although the ultimate proof of iron deficiency is the absence of stainable iron in bone marrow aspirates, this procedure is not routinely performed because it is painful and expensive. The proportion of reticulocytes usually is normal, but transient increases may follow acute hemorrhage or treatment with iron. The white cell and platelet count generally are normal.

Serum ferritin concentration is an early and specific indicator of body iron stores and is very useful in distinguishing iron deficiency from other causes of microcytic anemia. Ferritin concentrations fall in iron deficiency states but increase abnormally in iron storage conditions. Serum ferritin concentrations of less than 15 μg per liter (normal, 15–300 μg/L) generally are diagnostic for iron deficiency in adults. However, interpretation of ferritin levels entails consideration of other patient factors, such as coexisting inflammatory processes, liver disease, or malignancy. Ferritin is an acute phase reactant to inflammatory diseases such as rheumatoid arthritis or acute infection. In these conditions, serum ferritin concentrations increase, with the lower level of normal increasing to 50 μg per liter. Patients with levels between 12 μg per liter and 50 μg per liter should be investigated further for iron deficiency anemia.

Serum TfR measurement reflects the number of transferrin receptors on immature red cells and is an indication of bone marrow erythropoiesis. While ferritin is an early indicator of iron deficiency, TfR measurement provides information on the later stages of iron deficiency, increasing only after iron stores are depleted. It is not affected by inflammatory processes, and is useful in differentiating iron deficiency from anemia caused by chronic disease, infection, or inflammation. Use of the TfR to serum ferritin ratio has been advocated for earlier and more sensitive detection of iron deficiency.

Serum iron levels and the TIBC are other traditional measures for evaluating iron deficiency. However, these are less sensitive and more variable than ferritin determination and often are normal in the early stages of iron deficiency. A low serum iron with a high TIBC level generally is characteristic of iron deficiency. Normal to low serum iron levels with a normal or low TIBC is associated with anemias of chronic disease. In thalassemia, hemoglobinopathies, and sideroblastic

anemia, serum iron levels are normal or high. Transferrin saturation, another indicator of body iron stores, is below 16% in most cases of iron deficiency anemia. Transferrin saturation levels below 5% are found only in iron deficiency. However, there is considerable overlap with anemias of chronic disease.

Which tests are used to assess iron status depends on the patient's history and condition, the goal of the evaluation (early detection of iron depletion versus assessment of the existence or cause of an anemia), and laboratory equipment available. To check for anemia, Hb or Hct may be assessed, with other tests ordered if anemia is found. Monitoring iron depletion to prevent anemia includes using tests with sensitivity for the earlier stages of iron deficiency. Many clinicians use the ferritin test as the first-line test of iron status because it is an early indicator of iron store depletion. However, concurrent inflammatory or infectious processes or neoplasms reduce its reliability. Therefore, multiple tests often are used to assess iron status.

In the absence of a specialized hematology facility, a tentative diagnosis of iron deficiency can be made by giving a trial of iron therapy, and monitoring Hb concentrations and reticulocyte counts. Significant reticulocytosis occurs 7 to 10 days after the start of treatment, and the Hb concentrations increase over 3 to 4 weeks. Inflammatory disease may retard reticulocytosis.

Prevention

Prevention is accomplished by identifying high-risk patients and correcting iron deficiencies before anemia develops. Management is directed toward identifying and treating the underlying cause of the iron deficiency and correcting the iron deficiency with diet or supplementation.

Treatment

Although dietary improvements may reduce the risk of iron deficiency, the poor absorption of iron from foods limits the usefulness of dietary therapy in correcting an existing deficiency. Therefore, iron deficiency generally is corrected with oral or parenteral iron. A workup should be completed before therapy is initiated because indiscriminate iron administration can delay the diagnosis of underlying causes. Most iron therapy is given by the oral route, with few situations justifying the use of parenteral iron. With appropriate therapy, the Hb levels improve within a few weeks, and the patient feels better. Adequate iron must be supplied in the early stages of treatment to optimize the response.

Strategy of iron-deficiency anemia treatment

1. The treatment must continue till saturation of iron depot (normalization of ferritin plasma level)
2. Duration of the treatment is 3 months on average.
3. Criteria of treatment effectiveness:

- Increase of hemoglobin is 10 g/L in a week
- 7-10 day – increasing of reticulocytes
- 3-4 week – normalization of hemoglobin and erythrocytes
- 10-12 week – normalization of ferritin plasma level

Pharmacotherapy *(principles)*

1. Treatment must be carry on till saturation of iron depots in organism (normalization of ferritin level in blood)
2. Duration of treatment is 3 months in average.
3. Criteria of treatment effectiveness:

- The speed of hemoglobin increasing is 10 g/L in a weak
- 7-10 days – appearance of reticulocytic crisis
- 3-4 weeks – normalization of hemoglobin and erythrocytes levels
- 10-12 weeks – normalization of ferritin level in blood

Correction of etiological factors (treatment of diseases, which are accompanied by bleeding)

1. Diet enriched by iron
2. Treatment by iron containing medications:

- Elimination of iron deficiency and anemia
- Restoration of iron stores
- Treatment of relapses

Medications for treatment of iron-deficiency anemia

1. Iron preparations for oral use (daily dose should be 100-300 mg of elemental iron):

- Ferrous sulfate (TARDYFERON 256 mg equal 80 mg of elemental iron) 1-2 tab in a day
- Ferrous fumarate (HEFEROL 350 mg equal 115 mg of elemental iron) 2 tab 3 times a day
- Ferrous gluconate (FERRONAL 300 mg equal 35 mg of elemental iron) 2 tabs 3 times a day

2. Iron preparations for parenteral use (to patients who are unable to tolerate oral iron)

- Polysaccharide iron - FERRUM LEK 2 mL (100 mg) i.m. and 5 mL (100 mg) i.v.
- Iron dextran - DEXTRAFER 2 mL (100 mg) i.m.

Oral iron supplementation is safer, more convenient, and less expensive than parenteral therapy. Oral iron preparations are salt forms, which vary in elemental iron content, cost, and effectiveness. Iron absorption from ferrous salts is considered better than that from ferric salts.

The dosage of the iron product is based on the elemental iron content. In general, 30 to 40 mg daily elemental iron is used to treat iron deficiency states. Since only 10% to 20% of iron is absorbed, 200 to 400 mg of iron would result in absorption of approximately 40 mg elemental iron.

The most common side effects of oral iron therapy are epigastric distress, abdominal cramping, nausea, diarrhea, and constipation caused by gastric irritation. The reported incidence of these side effects ranges from 15% to 46% with daily dosing. These side effects appear to be dose related. Options for

minimizing these side effects include reducing the daily dose, taking the iron with food (at the expense of lower absorption), or changing to once-a-week dosing. Use of enteric-coated products to minimize gastrointestinal effects is not recommended because the coating prevents dissolution in the stomach, thus minimizing iron absorption. Iron therapy can cause the stools to appear black. Patients should be educated about differences between stool changes from iron and those associated with gastrointestinal bleeding.

Iron absorption may be reduced in patients with reduced gastric acid production or prior gastrointestinal surgeries. Antacids, histamine-2 blockers, and proton pump inhibitors may also decrease iron absorption.

Oral iron may be inadequate in patients who are intolerant to oral iron, noncompliant, have abnormal absorption due to surgery or gastrointestinal conditions, or significant blood loss. Parenteral iron may be necessary in these patients.

Most adverse reactions occur during or shortly after the test dose and range from mild transient reactions to life-threatening anaphylactic reactions. Mild reactions are generally transient and include dyspnea, headache, nausea, vomiting, flushing, itching, urticaria, fever, hives, and chest, abdominal, or back pain. Anaphylactic reactions are characterized sudden onset of respiratory difficulty or cardiovascular collapse. Emergency medications such as epinephrine and corticosteroids to treat the anaphylactic reaction should be readily available. Severe reactions can still occur during therapeutic administration even though the test dose was uneventful. Systemic reactions may also occur 1 to 2 days after iron dextran therapy. These delayed reactions may include myalgias, arthralgias, and back pain.

Iron preparations should not be used in conditions, such as hemochromatosis and hemosiderosis, that already signify iron overload. In thalassemia and anemic conditions with chronic inflammatory disease, such as rheumatoid arthritis, iron is contraindicated because these conditions have normal to high iron stores because of impaired use of iron. Care must be exercised in giving iron to alcoholic patients because of elevated iron stores.

Megaloblastic Anemias

Megaloblastic anemia is a subclass of the macrocytic anemias. Megaloblastic anemia is characterized by a lowered blood Hb mass because of reduced erythropoiesis secondary to defective DNA synthesis in the developing erythroid cells of the bone marrow. Nonmegaloblastic macrocytic anemias (those not resulting from disorders of DNA synthesis) are caused primarily by alcoholism, liver disease, and hypothyroidism. Deficiencies of vitamin B_{12} or folate are the major causes of megaloblastic anemia, followed by drug-induced interference, direct or indirect, with DNA synthesis or nutritional status.

It is important to distinguish anemia caused by B_{12} from folate deficiency to optimize treatment. A positive response (correction of anemia) to folate therapy does not confirm that folate deficiency was the cause of the anemia because folate supplementation can correct anemia caused by B_{12} deficiency. If this situation

occurs, the B_{12} deficiency continues and the neurologic and gastrointestinal effects of B_{12} deficiency may develop.

B_{12}-deficiency anemia – is the anemia, which is characterized by impaired synthesis of DNA in erythrocaryocytes due to deficiency of vitamin B12 and appearance of megaloblastic hemopoesis.

Like iron deficiency, B_{12} deficiency anemia is preceded by various stages of B_{12} depletion. Because the liver B_{12} stores are large (2–5 mg), B_{12} deficiency develops over many years, and the onset of symptoms tends to be gradual. In addition to affecting erythropoiesis, B_{12} deficiency results in neurologic and gastrointestinal manifestations.

These symptoms do not appear to correlate with the development of anemia and often occur without evidence of hematologic effects of B_{12} deficiency. More importantly, the neurologic damage is progressive and, if untreated, can be permanent.

Physiologic Importance of Vitamin B_{12}

Vitamin B_{12}, also known as cobalamin (Cbl), occurs in synthetic and biologically active forms. It is a cobalt-containing vitamin that cannot be synthesized by mammalian tissue. Therefore, it must be obtained via dietary intake or supplementation. Some bacterial synthesis of B_{12} occurs in the large bowel and the cecum, but there is no absorption at these sites.

Vitamin B_{12} Needs

The daily requirement for humans is 0.4 to 2.4 μg, and higher in pregnant and lactating mothers. Some diets, such as vegan, macrobiotic, or weight-reduction diets that drastically restrict food selection, may not meet the minimum daily needs. The total body stores amount to 2 to 5 mg, mainly in the liver. Thus, B_{12} deficiency takes years to develop.

Vitamin B_{12} Absorption and Metabolism

Vitamin B_{12}, particularly at the usual low levels in foods, is well absorbed from the gastrointestinal tract by an orderly sequence of events involving different binding proteins: R-proteins, IF, and TCII. The R-proteins, a group of high-affinity, B_{12}-binding glycoproteins, are produced predominantly by leukocytes and are present in a variety of biologic secretions, including gastric fluid, plasma, saliva, tears, milk, and bile. Their function is not fully understood. Although cobalamin can bind to R-proteins or IF, at the low gastric pH, binding to gastric R-proteins is favored. The relative binding of B_{12} also depends on the dosage and the amounts of R-protein and IF secreted. The cobalamin remains bound to R-proteins in the upper small intestine until pancreatic proteases, such as trypsin, partially degrade the complex, releasing B_{12}, which then binds to IF. IF, a specific B_{12}-binding glycoprotein, is synthesized and secreted by the parietal cells of the stomach. Its secretion parallels hydrochloric acid secretion. IF is released at the cell surface, and the vitamin is taken up by the enterocyte. Approximately 4 hours later, B_{12} exits the cells bound to transcobalamin.

Another mechanism for B_{12} absorption involves diffusion and not IF. This mechanism is biologically important only when large amounts are ingested and generally provides only small quantities of the vitamin. This mechanism is being explored as a potential method of providing oral B_{12} therapy to people with low levels of IF (pernicious anemia).

The daily cellular needs for B_{12} are low, and much of what is ingested is stored in the liver. Vitamin B_{12} is conserved in the body by enterohepatic recycling. Biliary excretion of B_{12} is much higher than excretion in urine or feces. Vitamin B_{12} and its analogs in bile are excreted bound to biliary R-protein. When the complex comes into contact with pancreatic enzymes in the upper small intestine, B_{12} and its analogs are released because of biliary R-protein degradation. Only B_{12} binds to fresh IF; the analogs are excreted in the feces. In addition to being the major route of B_{12} analog excretion, bile may play a role in enhancing B_{12} absorption. When the diet contains little or no B_{12}, as may be the case for strict vegans, biliary cobalamin is conserved to the extent that clinical deficiency may take up to 20 years to develop. When malabsorption occurs, as in pernicious anemia, endogenous and dietary B_{12} are lost and deficiency develops within 3 to 6 years. This accounts for the slow and insidious course of pernicious anemia.

Epidemiology

Occurrence

B_{12} deficiency becomes increasingly prevalent with advancing age. In people over age 65, the incidence ranges from 5% to 40.5% depending on the criteria used to define deficiency. Anemia is a later finding of B_{12} deficiency, so the deficiency often is diagnosed and treated before anemia develops.

Etiology

Causes of B_{12} deficiency include inadequate intake, malabsorption, B_{12} degradation, and inadequate B_{12} use. In developed countries, dietary causes are rare and may be important only in vegans (strict vegetarians who do not consume foods of animal origin, including milk, cheese, and eggs), breast-fed babies of vegan mothers, and people living in countries where poor nutrition is widespread. Most cases of deficiency are secondary to malabsorption associated with pernicious anemia, gastric lesions, gastrectomy, achlorhydria, and a number of small bowel disorders. Inadequate B_{12} use results from drug interactions, congenital or acquired enzyme deficiencies, and abnormal B_{12} binding proteins.

Pernicious Anemia

Pernicious anemia, defined as B_{12} malabsorption caused by the loss of gastric IF secretion, is thought to be the most common cause of B_{12} deficiency. The term “pernicious” is used because the anemia is insidious and progressive. Current evidence suggests that pernicious anemia is caused by an autoimmune reaction against gastric parietal cells. Most patients have increased levels of circulating antibodies, particularly those directed against parietal cells and IF.

The incidence of pernicious anemia is about 1% in the general population, with most cases occurring in people over 60 years of age. There is a distinctive racial and geographic distribution, with pernicious anemia more common in

temperate regions such as North America and northern Europe than in tropical countries. Juvenile pernicious anemia is less common. These patients often develop clinical features of B_{12} deficiency during the second decade of life. Inherited conditions leading to pernicious anemia in infancy or early childhood may be caused by a lack of IF or the production of abnormal IF by an otherwise normal stomach.

Gastric disorders, most commonly gastrectomy, are the second most common cause of vitamin B_{12} malabsorption. Complete gastrectomy results in an absolute deficiency of IF, and megaloblastic anemia develops 3 to 6 years after surgery unless supplementation is given. Partial gastrectomy is a variable cause of B_{12} deficiency. Deficiency is also possible if sufficient gastric mucosa has been destroyed by ingestion of corrosive chemicals, by tumors, or by chronic gastritis.

Even when the diet is adequate, some stomach abnormalities prevent the release of the vitamin from foods. These include atrophic gastritis, achlorhydria, vagotomy, partial gastrectomy, and the use of H_2-receptor antagonists and proton pump inhibitors.

Small intestine disorders are the third most common cause of B_{12} deficiency. Abnormal situations leading to malabsorption range from impaired transfer of the vitamin from R-protein to competition for luminal B_{12} or a low pH in the ileum.

Drug-induced B_{12} deficiency has been associated with a number of pharmacotherapeutic agents. Colchicine, *p*-aminosalicylic acid, neomycin, H_2-receptor blockers, proton pump inhibitors, and biguanide hypoglycemic agents decrease absorption of B_{12}. Agents that reduce B_{12} absorption in the ileum include ethanol and cholestyramine.

Clinical Presentation

Clinical manifestations reflect abnormalities of the blood, gastrointestinal tract, and nervous system.

Affection of hemopoetic system: complaints on general weakness, dizziness, buzzing in the ears, darkening in the eyes, palpitation and dyspnea, at physical examination – paleness of skin, frequently with yellowish tint, sometimes elevated body temperature, tachycardia, extrasystoles, muted heart sounds, apical systolic murmur, nonspecific changes on ECG.

Affection of digestive system: complaints on decreased appetite, sensation of heaviness in the epigastric region after food intake, belching, nausea, pain and burning in the tongue, at physical examination – tongue is smooth, red (Hunter's glossitis), other possible signs are aphtous stomatitis, atrophic stomatitis, atrophic gastritis, atrophic enteritis with malabsorption, enlargement of liver and spleen.

Affection of nervous system (funicular myelosis): complaints on weakness in the low extremities, numbness, at physical examination - impaired sensitivity, decreasing of tendon reflexes, atrophy of muscles of low extremities, impaired function of pelvic organs (incontinence of urination and stool). Psychiatric manifestations include impaired mentation, delirium, paranoia, psychosis, irritability, depression, and personality changes.

Gastrointestinal tract or neurologic changes may occur in the absence of hematologic changes.

In severe cases the peripheral blood smear exhibits severe macrocytic anemia, leukopenia with hypersegmentation of the polymorphonuclear cells, and thrombocytopenia.

Diagnosis

Early diagnosis of B_{12} deficiency relies on identifying risk factors for deficiency , obtaining a complete medical, dietary, and medication history, and assessing appropriate clinical laboratory tests. The goal is to prevent development of anemia or neurologic symptoms by early recognition and treatment of B_{12} deficiency.

Measurement of plasma B_{12} concentrations is simple and inexpensive and is considered the standard test for diagnosing B_{12} deficiency. Another alternative is measurement of TCII saturation, which decreases early in B_{12} deficiency. However, because only small amounts of B_{12} are bound to TCII, low levels of detection are needed that results in increased variability, thus limiting its clinical usefulness.

"Normal" B_{12} concentrations also occur despite an actual B_{12} deficiency in liver disease, myeloproliferative disorders, and nitrous oxide anesthesia. Cutoff points for normal B_{12} concentrations also vary, and symptoms do not always occur with low values. Recent studies have documented that asymptomatic patients with low B_{12} concentrations have metabolic abnormalities strongly suggestive of B_{12} deficiency at the cellular level, which reverse with B_{12} treatment.

Once B_{12} deficiency is determined, assessment of the cause (malabsorption vs. other) guides treatment selection. Antigastric parietal cell or anti-IF antibodies (IFAs) can be measured to provide information about a patient's ability to absorb B_{12}. Antigastric parietal cell antibodies often are found in patients with gastritis not affecting B_{12} absorption and, thus, are not sensitive or specific for assessing B_{12} absorption. However, IFAs rarely occur without B_{12} malabsorption and are found in 50% to 75% of patients with pernicious anemia.

A Schilling test (with or without IF) is an alternative method of assessing B_{12} malabsorption. Several types of Schilling tests are available. The standard test is divided into three stages. In stage I, an oral dose (1 μg for adults, 0.5–1 μg for children) of 57 Co-labeled B_{12} is given, followed by a 1-mg intramuscular dose of unlabeled B_{12}. The large intramuscular dose saturates B_{12}-binding proteins in the blood. Consequently, there are fewer binding sites for 57 Co-labeled B_{12}, and a substantial proportion is excreted in the urine. Urine is collected over 24 hours and the amount of labeled B_{12} measured. B_{12} absorption is considered to be impaired if less than 10% of the label is excreted in the urine. If less than 5% is excreted, the diagnosis is consistent with pernicious anemia.

Stage II of the test distinguishes between the possible causes of the malabsorption (e.g., pernicious anemia, lack of ileal absorptive sites, or bacterial overgrowth proximal to the terminal ileum). The same procedure is followed as in stage I except that IF is given with the radiolabeled B_{12}. If the B_{12} deficiency is

caused by lack of IF (pernicious anemia), stage I should be abnormal and stage II should be normal. If both stages are abnormal, an ileal disorder, bacterial overgrowth, pancreatic disorders, or fish tapeworm infestation may be causing B_{12} malabsorption. Stage III of the test, which involves giving the patient an antibiotic (usually tetracycline 250 mg orally four times a day for 10–14 days) and then repeating the stage I test, checks for possible bacterial overgrowth. The Schilling test depends on renal function and a complete 24-hour urine collection. Decreased renal function and incomplete urine collection lead to inaccurate results. In addition, H_2-antagonists and proton pump inhibitors may cause falsely abnormal results by preventing the degradation of R-protein and decreasing the secretion of endogenous IF. Conditions that reduce hydrochloric acid production (H_2-antagonists and proton pump inhibitors) and other situations in which acid and IF secretion are reduced (achlorhydria, complete or partial gastrectomy) can give falsely normal Schilling test results.

Anemia is a late presentation of B_{12} deficiency that may be avoided with early detection and correction of B_{12} depletion. Hematologic tests, such as a blood smear and the red cell indices, help differentiate the cause of anemia. Macrocytosis (MCV >100 fL) often occurs with B_{12} deficiency, but it also occurs with other conditions, such as liver disease, myxedema, acute myelogenous leukemia, acquired sideroblastic anemia, aplastic anemia, hemolytic anemia, posthemorrhagic states, splenectomy, and certain medications (e.g., zidovudine). Evaluating the smear for megaloblastic changes, such as neutrophil hypersegmentation and oval-shaped erythrocytes, generally differentiates a B_{12} or folate deficiency from other causes. If iron deficiency occurs along with B_{12} deficiency, the MCV may appear normal, but the blood smear should show megaloblastic and microcytic cells.

Treatment

Management includes identifying B_{12} deficiency early (before anemia or neurologic symptoms develop), correcting the cause of the deficiency if possible, replenishing depleted stores, and if necessary, administering maintenance B_{12} therapy. Once anemia or other symptoms develop, the aim of treatment is to reverse the symptoms (achieve hematologic remission, reverse or retard nervous system complications, and eliminate gastrointestinal symptoms) and replenish B_{12} stores.

1. The treatment must be initiated only after verification of diagnosis by myelogram.

2. Treatment includes i/m injections of vitamin B_{12} (cyanocobalamin 0,02% 1 ml or 0,05% 1 ml 1 time in a day).

3. Treatment course is 4-6 weeks.

4. In case of funicular myelosis, the dose of vitamin B_{12} increases twice as much.

5. Transfusions of erythrocytic mass are indicated only in case of life threatening emergencies (coma, hemoglobin less then 50 g/L, heart failure).

6. Treatment of vitamin B12 deficiency anemia should continue during whole life (i/m injections 2 times in the month).

7. Criteria of effectiveness of the treatment:

- Subjective improvement of self being at first few day of treatment.
- Reticulocytosis (to 20%) on 5-7 days from beginning of treatment

Increasing of hemoglobin and erythrocytes from 2 week of treatmentA debated area is use of oral B_{12} therapy in patients with impaired absorption (e.g., pernicious anemia, complete or partial gastrectomy). Because approximately 1% of an oral dose of B_{12} can be absorbed by a nonspecific, non– IF-dependent process, large oral dosages may provide sufficient B_{12} to correct the deficiency, replenish stores, and resolve symptoms.

Folate Deficiency

Folic deficiency anemia – is anemia, which is characterized by impaired synthesis of DNA in erythrocaryocytes due to deficiency of folic acid and appearance of megaloblastic hemopoesis..

Like B_{12} deficiency, folate deficiency occurs in stages, with depletion of stores leading to deficiency that can result in megaloblastic anemia and other hematologic abnormalities (thrombocytopenia, leukopenia). Treating a B_{12} deficiency megaloblastic anemia with folic acid may correct the anemia, but does not correct the B_{12} deficiency or prevent the development of neurologic changes. Therefore, it is important to determine the cause of a megaloblastic anemia before initiating therapy. Folate also is critical in early pregnancy for fetal neural tube development.

Physiologic Importance of Folate

Reduced forms of folate (tetrahydrofolate) are cofactors for transformylation reactions in the biosynthesis of purines and thymidylates of nucleic acids. In folate deficiency, reduced thymidylate synthesis leads to defective DNA synthesis, resulting in megaloblast formation and bone marrow suppression. Folate is also involved in the methylation cycle and is essential in providing methyl groups for a wide range of cellular methyltransferases. In particular, folate is needed in Hcy metabolism, which accumulates in folate deficiency.

Folate Needs

Folate needs depend on metabolic and cell turnover rates. In general, the minimum daily requirement is 65 to 400 μg daily. In pregnancy, 600 μg daily is recommended, and 500 μg daily for lactating mothers.57,80 More than 2% is degraded daily, so a continuous dietary supply is essential. The average amount stored in the body is 5 to 10 mg, one half of which is found in the liver. With folate depletion, deficiency leading to anemia generally occurs within 6 months.

Folate Absorption and Metabolism

Folate is a water-soluble vitamin found in many plant and animal foods. Dietary sources are primarily polyglutamates, which must be converted to the monoglutamate form for absorption. This process often is impaired in malabsorption syndromes, such as sprue. The percentage of dietary folate absorbed

depends on the source, with liver, yeast, and egg yolk having high absorption; only 10% of most other dietary sources are absorbed. Active absorption of dietary folate occurs mainly in the proximal part of the small intestine. Synthetic folate (folic acid) is already in the monoglutamate form and has greater stability and better absorption (almost twice the bioavailability) than dietary folate. Folic acid from pharmaceutical products is almost completely absorbed in the upper duodenum, even in the presence of malabsorption.

Amounts of folic acid beyond the daily needs are excreted almost entirely as metabolites by the kidney.

Epidemiology

Inadequate diet, alcoholism, and pregnancy are the most common causes of folate deficiency. Other causes include increased requirements, malabsorption, enhanced metabolism, and interference in the metabolism or clearance by other pharmacotherapeutic agents.

Malnutrition is often a significant cause of folate deficiency. Folate-rich foods include raw spinach, broccoli, cauliflower, peanuts, and peas. Folate is highly susceptible to cooking or processing. Heating foods (microwaving or boiling) decreases the amount of folate available by up to 50%. People at risk of inadequate folate intake include alcoholics whose main caloric intake is in the form of ethanol, narcotic addicts who have a poor diet, older adults who often do not feel like eating or who eat commercially prepared foods, institutionalized people who have no control over their diet, adolescents who may skip meals and eat junk foods, and pregnant women who have increased needs, that often are not met by dietary intake.

Folate needs increase during malignancy, increased erythropoiesis, and conditions causing rapid cell turnover. Folate deficiency is very common in myeloproliferative disorders, such as chronic myeloid leukemia and myelofibrosis, often leading to thrombocytopenia or anemia. The increased folate needs in chronic hemolytic anemia, exfoliative dermatitis, generalized psoriasis, or extensive burns can also lead to folate deficiency. In these cases, adequate supplementation is needed. Anemia is more likely to occur if several contributing factors are present.

Various drugs can affect folate absorption, metabolism, and use. Folate supplementation generally is not necessary during short courses of these drugs (e.g., oral sulfonamide antibiotics).

Clinical Presentation

Signs and symptoms of folate deficiency are similar to those of other anemias. In addition, megaloblastosis, glossitis, diarrhea, and weight loss may occur.

Diagnosis

As with B_{12} deficiency, early diagnosis and prevention of anemia depend on identification and treatment of high-risk patients. Serum or erythrocyte folate concentrations may be determined to assess folate status. Within 5 weeks of inadequate folate intake, the serum folate concentration declines to the subnormal

range, whereas the erythrocyte folate concentration does not decline until about 3 months.

In the later stages of folate deficiency, a blood smear and hematologic evaluation often show macrocytosis with megaloblastosis. Megaloblastosis must be interpreted in light of B_{12} status because of similar findings in B_{12} deficiency. Erythrocyte folate and serum B_{12} concentrations should be measured. Anemia occurs only when tissue levels are depleted, so a normal serum folate concentration does not exclude deficiency.

Treatment

The primary prevention of folate deficiency, and hence anemia, should occur through dietary manipulation or oral supplementation.

Hemolytic Anemia

Hemolytic anemias – is group of inherited and acquired diseases, which is characterized by hemolytic syndrome – excessive destruction of erythrocytes.

Depending on localization of hemolysis anemias can be with intracellular hemolysis (in the macrophages) and with intravascular hemolisis (in the lumen of vessels)

The anemia is of greatest clinical concern when the rate of RBC destruction exceeds that of erythropoiesis. The hemolytic process may occur chronically or manifest as an acute episode, depending on the etiologic mechanism. Acute hemolysis is generally a more clinically threatening event. Many anemias have a hemolytic component due to the production of defective or damaged RBCs (e.g., megaloblastic anemias, thalassemias, sickle cell anemia). As there are a multitude of causes of hemolytic anemia, this section will focus on those amenable to specific medical treatment and those that are drug-induced.

Etiology.

Hemolytic anemias can be categorized as either inherited or acquired disorders. Inherited hemolytic anemias include defective globin synthesis, erythrocyte membrane defects, and erythrocyte enzyme deficiencies. Acquired hemolytic disorders are those caused by some extrinsic event and do not involve a genetic component. Typically, the acquired hemolytic anemias are either immune-mediated, due to physical stress on the RBC, or are induced by certain infections.

Etiology of hemolytic anemias

Hereditary factors:

Impaired structure of erythrocytes membrane.
Impaired activity of erythrocytes enzymes.
Impaired synthesis of erythrocytes.

Acquired factors:

Autoimmune mechanisms (autoimmune hemolytic anemia).
Somatic mutations of steam cell (paroxysmal nocturnal hemoglobinuria).
Influence of medications.
Traumatic injury of erythrocytes in cardiovascular system.
Influence of hemolytic poisons, chemical agents, bacterial toxins.

Pathogenesis of hemolytic anemia

Influence of the etiological factors leads to injury of erythrocytes membranes and hemolysis. The mechanisms depend on etiological factor (decreasing of osmotic resistance of erythrocytes – in case of inherited microspherocytosis, production of antierythrocytic antibodies – in case of autoimmune hemolytic anemia etc).

Epidemiology

The prevalence and distribution of sickle cell anemia and thalassemia have been discussed previously. With respect to other inherited hemolytic disorders, the incidence of hereditary spherocytosis and hereditary elliptocytosis in the United States is approximately 220 and 400 per million, respectively. Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common inherited erythrocyte enzyme disorder worldwide, affecting close to 200 million people, but not all patients with G6PD deficiency are significantly predisposed to oxidative hemolysis.

Classification of Common Hemolytic Anemias

I. Inherited

Globin synthesis defect

Sickle cell anemia

Thalassemia

Unstable hemoglobin disease

Erythrocyte membrane defect

Hereditary spherocytosis

Hereditary elliptocytosis

Hereditary stomatocytosis

Erythrocyte enzyme defect

Hexose-monophosphate shunt defect (e.g., glucose- 6-phosphate dehydrogenase)

Glycolytic (Embden-Meyerhof) enzyme defect (e.g., pyruvate kinase)

Other enzyme defect (e.g., adenylate kinase)

II. Acquired

Immune-mediated

Warm reacting antibody (IgG)

Primary (Idiopathic)

Secondary (e.g., collagen vascular disease, lymphoproliferative disorders)

Drug-induced

Cold agglutinin disease (IgM)

Acute (e.g., *Mycoplasma* pneumonia, infectious mononucleosis)

Chronic (e.g., lymphoid neoplasms, idiopathic)

Paroxysmal nocturnal hemoglobinuria

Transfusion reactions

Hemolytic disease of newborns

Microangiopathic and traumatic
Disseminated intravascular coagulation
Hemolytic-uremic syndrome
Thrombotic thrombocytopenic purpura
Prosthetic or diseased heart valves
Infection
Exogenous substances
Other
Liver disease
Hypophosphatemia

The majority of acquired hemolytic anemias are idiopathic. Many are due to immune reactions, collagen vascular disease, or malignancy. Drugs are the causative agents in 10% of cases.

Pathophysiology

The average RBC life span is 120 days, but during severe hemolytic episodes this can be reduced to as low as 5 to 20 days. RBCs are hemolyzed either within the circulation (intravascular hemolysis) or taken up by the RES and destroyed (extravascular hemolysis). Intravascular hemolysis may be caused by trauma to the RBC, complement fixation to the RBC (immune-mediated), or exposure to exogenous substances. Under normal circumstances, however, most RBC catabolism occurs extravascularly by the RES in the liver and spleen. Specific drug-induced mechanisms of RBC hemolysis are discussed later in the context of G6PD deficiency and immune-mediated hemolysis.

Following lysis of the RBC, hemoglobin is released into the blood, where it is bound by the plasma protein haptoglobin. Free heme molecules are bound by the plasma protein hemopexin. The hemoglobin–haptoglobin complex is rapidly cleared from the circulation by the RES, and the heme component is metabolized to unconjugated (indirect) bilirubin. In the liver, this is linked with glucuronic acid, forming conjugated (direct) bilirubin, which passes from the bile duct into the intestine. Fecal bacteria then metabolize conjugated bilirubin to urobilinogen, which is primarily excreted in the feces. Iron from heme catabolism is stored as ferritin or hemosiderin.

During hemolysis, if the haptoglobin binding capacity is exceeded, unbound hemoglobin levels increase, resulting in hemoglobinemia. In this case, free hemoglobin is filtered through the glomerulus and is usually reabsorbed by the proximal tubules. In severe intravascular hemolysis, the reabsorptive capacity is exceeded, causing hemoglobinuria. Also during severe intravascular hemolysis, some heme molecules in the circulation are transferred from hemopexin to albumin, forming methemalbumin. When the liver's conjugating capacity is exceeded during moderate or severe hemolysis, unconjugated (indirect) bilirubin serum levels increase.

Clinical Presentation and Diagnosis

The primary diagnostic features of hemolytic anemia are a marked reticulocytosis and jaundice (including scleral icterus) due to hyperbilirubinemia. A corrected reticulocyte count >0.025 (2.5%) is a typical response to hemolysis. The severity of the anemia may also be judged by the extent to which the hematocrit is decreased. The enzyme lactate dehydrogenase (LDH) is released from the RBC during hemolysis, and plasma levels may be elevated. RBC membranes may sustain incomplete damage, resulting in the formation of spherocytic-shaped erythrocytes. These cells have an increased susceptibility to splenic removal. Splenomegaly is usually present in cases of chronic hemolysis.

Common Diagnostic Features of Hemolytic Anemia

1. Jaundice without inching of skin. Color of the skin is yellow with pallor.
2. Normochromic anemia (exclusions are hypochromic anemia in case of thalassemia and erythropoetic prothoporphiria).
3. Significant reticulocytosis in peripheral blood.
4. Presence of nuclear-containing erythroid cells (normocytes).
5. Irritation of the erythroid line (increasing of the erythrocaryocytes in the bone marrow higher than 25%).
6. Elevated level of the nonconjugative bilirubin.
7. Dark color of the urine due to appearance of urobilin (or appearance of hemoglobin in case of paroxysmal nocturnal hemoglobinuria).
8. Dark color of the stool due to elevated stercobilin.
9. Elevation of free hemoglobin (in case of intravascular hemolysis).
10. Enlargement of the spleen (in case of intracellular hemolysis).
11. Decreasing of life span of erythrocytes (test with radioactive chrome).
12. Elevation of plasma iron.
13. Low level of haptoglobin in the blood.

With respect to immune-mediated hemolysis, diagnostic evaluation includes the direct antiglobulin test (DAT or Coombs' test), which detects the presence of IgG or C3 (complement) on the surface of RBCs. Patients may have positive DAT results without hemolysis (up to 15% of hospitalized patients). Therefore, this must be correlated with other clinical evidence of a hemolytic process. The indirect antiglobulin test (IAT or indirect Coombs' test) detects the presence of antibodies against RBCs in the serum rather than on the surface of the RBC itself. This test is most commonly used in blood banks for antibody screening and cross-matching blood for transfusion. During oxidative hemolytic anemias, denatured hemoglobin precipitates within the RBC, forming Heinz bodies, which are visible during microscopic examination. Heinz bodies are rapidly removed by the spleen, creating “bite” cells, which are erythrocytes that appear to have a bite of cytoplasm removed.

Hereditary spherocytosis, elliptocytosis, and stomatocytosis are all genetic disorders inherited in an autosomal dominant fashion and are associated with

altered RBC morphology. Hemolysis and clinical sequelae tend to be more pronounced with hereditary spherocytosis than with the other two. Splenectomy usually corrects anemia in these individuals. Supplemental folic acid therapy (1 mg daily) is also recommended. Sickle cell anemia and thalassemia may also be considered inherited hemolytic anemias.

Treatment

Withdrawal or avoidance of any potentially oxidant drugs or other substances is the most important component of treatment.

Treatment of inherited hemolytic anemias

Hereditary spherocytosis – inherited disease due to defect of membranes of erythrocytes. In this disease erythrocytes have spherical shape and they may be destroyed easily by macrophages in the spleen.

Treatment: the most effective method is spleenectomy.

- Sickle cell anemia – disease with inherited impairment of hemoglobin synthesis (appearance of hemoglobin S with decreased solubility – HbS), which is characterized by abnormal shape of erythrocytes and hemolysis.

  Treatment: mean method – transfusions of packed red blood cells.
- Thalassemias are a heterogeneous group of inheretid hemoglobinopathies characterized by defect in the synthesis of one or more globin chain subunits.

Treatment: homozygotes – transfusions of packed red blood cells or spleenectomy in severe cases. For heterozygotes β-thalassemia – treatment is not required.

Treatment of the acquired hemolytic anemias

- Autoimmune hemolytic anemias are those due to production of antibodies to own erythrocyte antigenes.

Treatment: mean method – administration of glucocorticoids. The other possible methods are splennectomy, administration of cytostatics, transfusions of packed red blood cells, plasmopheresis.

Treatment of hemolytic crisis:

1. Replacement of circulating volume of blood.
2. Neutralization of toxic agents and stimulation of diuresis.
3. Elimination of acidosis.
4. Plasmopheresis, hemodialysis.
5. Administration of glucocorticoids.
6. Transfusions of packed red blood cells (in case of Hb<50 g/L.

Aplastic Anemia

Hypoplastic (aplastic) anemia – is the disease of hemopoetic sisteme characterized by suppression of hemopoesis (reduction of the erythroid, myeloid and megacaryocytic lines of the bone marrow), by development of pancytopenia and fatty degeneration of the bone marrow.

Aplastic anemia is distinguished by hypocellularity of the bone marrow and subsequent pancytopenia that is unrelated to malignancy or myeloproliferative

disease. The characteristic anemia, neutropenia, and thrombocytopenia result from failure of the pluripotential stem cell due to congenital or acquired processes. Although the causative mechanisms remain unknown, advances in therapy have greatly improved the overall prognosis.

Etiology

I. Chemical factors (benzol, arsenic, benzine, heavy metals, insecticides, pesticides etc.)
II. Physical factors (ionizing radiation and roentgenographic radiation)
III. Medications (antibiotics, sulfaniamides, nonsteroid anti-inflammatory drugs, gold preparations, cytostatics, antispasmodic drugs, antiarrhythmic drugs, oral hypoglycemic medications, antihypertensive drugs, antithyroid drugs)
IV. Infectious agents (viruses, micobacteria tuberculosis, fungi)
V. Immune diseases (rejection of transplantant, eosinophilic fasciitis, thymoma and carcinoma of thymus)

Although many causes have been identified, the majority of cases of aplastic anemia are classified as idiopathic. Myelosuppression is a component of several congenital diseases but is more commonly acquired after exposure to drugs, chemicals, ionizing radiation, or viruses. Aplastic anemia and paroxysmal nocturnal hemoglobinuria are closely associated; aplastic anemia may precede or progress to paroxysmal nocturnal hemoglobinuria.

Epidemiology

The annual incidence of aplastic anemia in the West is estimated to be two to five cases per million population.11 The prevalence of disease is higher in developing countries, perhaps reflecting increased exposure to viral hepatitis and environmental toxins. Two peaks are evident in the distribution of ages of onset: approximately 25% of those affected are under 20 years of age, and one third are over 60 years of age.

Pathophysiology

In normal hematopoiesis, three cell lines originate from the pluripotential stem cell, producing erythrocytes, granulocytes, and platelets. Both cellular and humoral factors regulate the stem cells to maintain a balance between self-replication and differentiation into particular cell types. Aplastic anemia develops when hematopoiesis is interrupted because of deficient or defective stem cells. In addition to reduced numbers of progenitor cells, suggested pathophysiologic mechanisms include immune-mediated suppression of stem cell function, disturbances in the bone marrow microenvironment, and alterations in the cellular or humoral interactions that normally sustain hematopoiesis. Research with a variety of treatment modalities supports T-cell–mediated destruction of marrow cells as the most likely cause of the majority of cases of acquired aplastic anemia.

Clinical Presentation

Anemic syndrome: complains on general weakness, tiredness, palpitation and dyspnea at physical exertion, dizziness, darkening in the eyes, at physical

examination – paleness of skin, yellowish tint of scleras, slightly increased spleen, muted heart sounds, apical systolic murmurs, nonspecific changes on ECG.

Hemorrhagic syndrome: complains on bleeding, at physical examiation – hemorrhagic lesions of skin predominantly on shins, thighs, abdomen, face. Extensive hematomas appear on the place of injections. In severe cases there are nasal, gastrointestinal, renal, pulmonary, uterine and intracerebral bleedings.

Predisposition to infectious inflammatory processes (tonsilitis, pneumonia etc.) due to deficiency of granulocytes.

Diagnosis

Diagnosis of aplastic anemia depends on the presence of at least two of the following measurements in the peripheral blood: hemoglobin less than <100 g/L, platelet count less than 50×10^9/L, and neutrophil count $<1.5 \times 10^9$/L. Severe aplastic anemia is further defined as even lower neutrophil, platelet, and reticulocyte counts, with marked bone marrow hypocellularity. Differentiation of aplastic anemia from other syndromes accompanied by hypocellularity, such as hypoplastic myelodysplasia, may be difficult.

Treatment

1. Administration of glucocorticoids (prednisolone per os 60-120 mg in a day).
2. Administration of anabolic drugs (retabolil 100 mg [2 ml] i/m 1 time in a week).
3. Treatment by androgenes – for males (testosterone 5% 1 ml в/м 2 times a day).
4. Administration of cytostatics (azathioprine 50 mg per os 3 times a day)
5. Spleenectomy (if glucocorticoids are not effective).
6. Treatment by antilymphocytic globulin.
7. Administration of ciclosporin (100 mg per os 2 times a day).
8. Bone marrow transplantation.
9. Treatment by colony stimulating factors (filgrastim i/v 10 μg/kg/day).
10. Transfusions of packed red blood cells.
11. Administration of deferoxamine (500 mg i/m 1 time a day).
12. Transfusions of thrombocytes.
13 Treatment by immunoglobulin.

QUESTIONS.

1. What is the average life span of an erythrocyte?
A. 3 days
B. 15 days
C. 30 days
D. 90 days
E. 120 days

2. What is the average amount of circulating blood of a person weighting 70 kg?
A 6.5 l
B. 8.5 L
C. 4.5 L
D. 2.5 L
E. 0.5 liters

3. Which of the ratios reflects the hematocrit?
A ratio of the number of erythrocytes and leukocytes
B. ratio of blood cells and plasma volume
C. ratio of platelets and plasma volume,
D. ratio of the number of granulocytes and lymphocytes
E. ratio of albumin and globulin

4. What is the function of the bone marrow?
A hematopoiesis
B. transport
C. endocrine
D. detoxication
E. protection

5. What is the meaning of color index in the clinical analysis of blood?
A. the amount of hemoglobin
B. erythrocyte hemoglobin saturation
C. color of arterial blood
D. color of venous blood
E. the number of red blood cells

6. What is a reticulocyte?
A. young lymphocytes
B. young monocytes
C. stab leukocytes
D. young erythrocytes
E. young eosinophils

7. Which process contributes to the concave shape of red blood cells and the lack of its nucleus?
A hemagglutination
B. chemotaxis
C. proliferation
D. gas exchange
E. thrombosis

8. What are the most common cells per unit volume of blood?
A leukocyte
B. platelet
C. erythrocytes
D. lymphocytes
E. granulocytes

9. Which hormone controls the proliferation and maturation of erythroid cells?
A. thrombopoietin
B. thyroxine
C. adrenaline
D. testosterone
E. Erythropoietin

10. What is the hemolysis?
A breakdown of red blood cells
B. hemorrhagic rash
C. destruction of red blood cells nuclei
D. formation of hemoglobin
E. increase of indirect bilirubin in the blood plasma

Control of the final level of knowledge.

1. These etiological factors contribute to iron deficiency anemia, but one?
A. significant blood loss during menstruation
B. malnutrition
C. multiple pregnancy and childbirth
D. resection of the small intestine
E. the use of fatty and fried foods

2. The sideropenic syndrome is characterized by all, except one:
A. muscle weakness
B. the affection of the mouth
C. pale skin
D. inlarged liver
E. dysphagia

3. What is hemoglobin characteristic of mild iron deficiency anemia?
A. Hemoglobin 90-120 g / l
B. Hemoglobin 70-90 g / l
C. Hemoglobin <70 g / l
D. hemoglobin 110-120 g / l
E. Hemoglobin 120-130

4. How to describe anemia, in which the value of the color index greater than 1.05?
A normochromic
B. microcytic
C. macrocytic
D. hyperchromic
E. hypochromic

5. What is the anisocytosis?
A. the presence of red blood cells of different shapes
B. the presence of very small particles of red blood cells
C. presence of red blood cells of different sizes
D. presence of erythrocytes with different color
E. the presence of red blood cells, similar to the ring

6. The folic acid deficiency anemia is characterized by all, except one:
A hyperchromic anemia
B. macrocytosis
C. atrophic gastritis
D. pale skin
E. General weakness

7. Which variant of the nervous system impairment is characteristic for B12-deficiency anemia?
A. encephalopathy
B. hemiparesis
C. hemiplegia
D. Sydenham's chorea
E. funicular myelosis

8. Which method is used for the treatment of autoimmune hemolytic anemia?
A. splenectomy
B. Bone marrow transplantation
C. red cell transfusion
D. Treatment with glucocorticoids
E. Plasmapheresis

9. For aplastic anemia is characterized by all except one:
A hyperchromic anemia
B. Thrombocytopenia
C. Leukopenia

D. Increased ESR
E. Reduction of reticulocytes

10. Which criterion is crucial for assessment of severity of the patient with acute bleeding?
A. Dynamics of heart rate and blood pressure
B. The level of hemoglobin
C. change in color of skin
D. the level of red blood cells
D. the value of hematocrit

Case based questions:

Task 1

A 55-year-old male is being evaluated for constipation. There is no history of prior gastrectomy or of upper GI symptoms. Hemoglobin is 10 g/dL, mean corpuscular volume (MCV) is 72 fL, serum iron is 4 mg/dL (normal is 50 to 150 mg/dL), iron-binding capacity is 450 mg/dL (normal is 250 to 370 mg/dL), saturation is 1% (normal is 20 to 45%), and ferritin is 10 mg/L (normal is 15 to 400 mg/L). The next step in the evaluation of this patient's anemia is

a. Red blood cell folate
b. Iron absorption studies
c. Colonoscopy
d. Bone marrow examinaton

Task 2

A 35-year-old female who is recovering from *Mycoplasma* pneumonia develops increasing weakness. Her Hgb is 9.0 g/dL and her MCV is 110.

The best test to determine whether the patient has a hemolytic anemia is

a. Serum bilirubin
b. Reticulocyte count and blood smear
c. *Mycoplasma* antigen
d. Serum LDH

Task 3

After undergoing surgical resection for carcinoma of the stomach, a 60-year-old male develops numbness in his feet. On exam, he has lost proprioception in the lower extremities and has a wide-based gait and positive Romberg sign. A peripheral blood smear shows macrocytosis and hypersegmented polymorphonuclear leukocytes. The neurologic dysfunction is secondary to a deficiency of which vitamin?

a. Folic acid
b. Thiamine
c. Vitamin K
d. Vitamin B12

Task 4

A 38-year-old female presents with recurrent sore throats. She is on no medications, does not use ethanol, and has no history of renal disease.

Physical exam is normal. A CBC shows Hgb of 9.0 g/dL, MCV is 85 fL (normal), white blood cell count is 2,000/mL, and platelet count is 30,000/mL.

The best approach to diagnosis is

a. Erythropoietin level

b. Serum B12

c. Bone marrow biopsy

d. Liver spleen scan

Task 5

A 20-year-old black male with sickle cell anemia (SS homozygote) has had several episodes of painful crises. The least likely physical finding in this patient is

a. Scleral icterus

b. Systolic murmur

c. Splenomegaly

d. Ankle ulcers

Task 6

A 36-year-old African-American woman with systemic lupus erythematosus presents with the acute onset of lethargy and jaundice. On initial evaluation, she is tachycardic, hypotensive, appears pale, is dyspneic, and is somewhat difficult to arouse. Physical examination reveals splenomegaly.

Her initial hemoglobin is 6 g/dL, white blood cell count is 6300/mL, and platelets are 294,000/mL. Her total bilirubin is 4 g/dL, reticulocyte count is 18%, and haptoglobin is not detectable. Renal function is normal, as is urinalysis. What would you expect on her peripheral blood smear?

A. Macrocytosis and PMN's with hypersegmented nuclei

B. Microspherocytes

C. Schistocytes

D. Sickle cells

E. Target cells

Task 7

You are investigating the cause for a patient's anemia. He is a 50-year-old man who was found to have a hematocrit of 25% on routine evaluation. His hematocrit was 47% 1 year ago. Mean corpuscular volume is 80, mean corpuscular hemoglobin concentration is 25, mean corpuscular hemoglobin is 25. Reticulocyte count is 5%. Review of the peripheral blood smear shows marked numbers of polychromatophilic macrocytes. Ferritin is 340 mg/L. What is the cause of this patient's anemia?

A. Defective erythroid marrow proliferation

B. Extravascular hemolysis
C. Intravascular hemolysis
D. Iron-deficiency anemia
E. Occult gastrointestinal bleeding

Task 8

All the following are associated with pure red cell aplasia *except*
A. anterior mediastinal masses
B. connective tissue disorders
C. giant pronormoblasts
D. low erythropoietin levels
E. parvovirus B19 infection

Task 9

All of the following laboratory values are consistent with an intravascular hemolytic anemia *except*
A. increased haptoglobin
B. increased lactate dehydrogenase (LDH)
C. increased reticulocyte count
D. increased unconjugated bilirubin
E. increased urine hemosiderin

Task 10

A 23-year-old man presents with diffuse bruising. He otherwise feels well. He takes no medications, does not use dietary supplements, and does not use illicit drugs. His past medical history is negative for any prior illnesses. He is a college student and works as a barista in a coffee shop. A blood count reveals an absolute neutrophil count of 780/μL, hematocrit of 18% and platelet count of 21,000/μL. Bone marrow biopsy reveals hypocellularity with a fatty marrow. Chromosome studies of peripheral blood and bone marrow cells are performed which exclude Fanconi's anemia and myelodysplastic syndrome. The patient has a fully histocompatible brother. Which of the following is the best therapy?
A. Anti-thymocyte globulin plus cyclosporine
B. Glucocorticoids
C. Growth factors
D. Hematopoietic stem cell transplant
E. Red blood cell and platelet transfusion

Further reading:

1. Principles of Harrison's internal medicine, self-assessment and board review 17th editon /Edited by Charles Wiener, The McGraw-Hill Companies, Inc. – 2008. – 490 p.
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3. USMLE Step 2 Clinical Knowledge / Edition Kaplan inc. – 2005. - 548 p.
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5. Davidson's principles of medicine, 20th edition / Edited by Nicholas A. Boon, Nicki R. Colledge, Brian R. Walker. Elsevier Limited – 2006. – 2456 p.
6. Cecil Medicine, 23rd edition / Edited by Lee Goldman, Dennis Ausiello. Saunders Elsevier. – 2007. – 2178 p.
7. Kumar & Clark: Clinical Medicine, 6th edition / Edited by Parveen Kumar, Michael Clark. Elsevier, Inc. – 2006. – 1862 p.