Ministry of Education and Science of Ukraine
Ministry of Health of Ukraine
Sumy State University

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INTERNAL MEDICINE: HEMATOLOGY

Study guide

Under the editorship of V. F. Orlovsky, N. V. Demikhova

Recommended by the Academic Council of Sumy State University

Sumy
Sumy State University
2019

УДК 616.15(075.8)
V99

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Recommended for publication
by the Academic Council of Sumy State University
as a study guide
(minutes № 4 of 18.10.2018)

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V99 Internal Medicine: Hematology : study guide / L. B. Vynnychenko, L. N. Prystupa, O. M. Chernatska ; under the editorship of V. F. Orlovsky, N. V. Demikhova. – Sumy : Sumy State University, 2019. – 136 p.
ISBN 978-966-657-751-4

In this study guide there is the presentation of up-to-date data of etiology, pathogenesis, diagnostic and treatment criteria of hematological diseases such as anemia, hemoblastosis, lymphadenopathy, splenomegaly, hemorrhagic diathesis, disseminated intravascular coagulation syndrome, etc.

The study guide is designed for senior students, interns, masters, postgraduate students and clinical interns in the specialties "Therapy", "General practice – family medicine".

УДК 616.15(075.8)

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Introduction

The publication of a study guide on hematology is conditioned by the increasing prevalence of blood system diseases. This situation is associated with certain environmental changes in Ukraine, the negative impact of environmental factors on the human body such as ionizing radiation and chemicals that are widely used both in agriculture and food industry.

The manual highlights the current views on the etiology, pathogenesis, clinic, diagnosis, differential diagnosis and treatment of blood disorders. Considerable attention is paid to anemia, since it is the most common syndrome in the practice of doctors of various specialties.

Significant progress has been made in the diagnosis and treatment of hemoblastoses, which is also reflected in this manual.

The release of this study guide is determined by the lack of awareness and alertness of the students and general practitioners in the diagnosis and treatment of hematological diseases, lack of textbooks devoted to this branch of medicine.

Section I. ANEMIAS

Anemia is a decrease in the number of red blood cells (RBCs), hematocrit, or hemoglobin (Hb) level in the blood. The RBC mass represents the balance between production and destruction or loss of RBCs.

Anemia is a condition developed when your blood lacks enough healthy RBCs. These cells are the main transporters of oxygen into organs. If RBCs are also deficient in Hb, then your body isn't getting enough oxygen. Anemia is the most common blood condition in the United States. It affects about 3.5 million Americans. Women and people with chronic diseases are refered to increased risk of anemia (Tables 1, 2, and 3).

The three main causes of anemia are:

1. Blood loss
2. Deficient erythropoiesis
3. Excessive hemolysis (RBC destruction).

Table 1 ─ **Classification of anemia by cause**

Mechanism	Examples
Blood loss	
Acute	- gastrointestinal (GI) bleeding - Injuries - Childbirth - Surgery
Chronic	- Bladder tumors - Cancer or polyps in gastrointestinal tract - Heavy menstrual bleeding - Kidney tumors - Ulcers in the stomach or small intestine

Table 2 ─ **Deficient erythropoiesis**

Mechanism	**Examples**
Microcytic	- Iron deficiency - Iron-transport deficiency - Defective iron utilization - Defective iron reutilization - Thalassemias (also classified under excessive hemolysis due to intrinsic RBC defects)
Normocytic-Normochromic	- Aplastic anemia - Hypoproliferation - Chronic kidney disease - Endocrine disorders (thyroid, pituitary) - Protein depletion - Myelodysplasia - Myelophthisis
Macrocytic	- Copper deficiency - Folate deficiency - Vitamin B12, Vitamin C deficiency

Table 3 ─ **Excessive hemolysis due to extrinsic RBC defects**

Mechanism	Examples
Reticuloendothelial hyperactivity with splenomegaly	- Hypersplenism
Immunologic abnormalities	- Autoimmune hemolysis - Cold antibody hemolysis (paroxysmal cold hemoglobinuria) - Warm antibody hemolysis - Isoimmune (isoagglutinin) hemolysis
Mechanical injury	- Infection - Trauma
Membrane alterations, acquired	- Hypophosphatemia - Paroxysmal nocturnal hemoglobinuria - Stomatocytosis
Membrane alterations, congenital	- Membrane alterations, congenital
Metabolic disorders (inherited enzyme deficiencies)	- Embden-Meyerhof pathway defects - glucose-6-phosphate dehydro-genase (G-6-PD) deficiency
Hemoglobinopathies	- HbC, HbE, and HbS/C diseases - Hb S─β-thalassemia disease - Sickle cell disease (Hb S) - Thalassemias (β, β-δ, and α)

1.1. IRON DEFICIENCY ANEMIA (ANEMIA OF CHRONIC BLOOD LOSS. CHLOROSIS)

Iron deficiency is the most common cause of anemia and it is usually a result of blood loss. Symptoms are usually nonspecific. RBCs tend to be microcytic and hypochromic, and iron stores are low as shown by low serum ferritin and low serum iron levels with high serum total iron binding capacity. If the diagnosis is made, occult blood loss is suspected. Treatment involves iron replacement and treatment of the cause of blood loss.

Pathophysiology

Iron deficiency anemia (IDA) occurs when your body doesn't have enough iron. Iron is important because it helps you get enough oxygen throughout your body. Your body uses iron for making Hb. Hb is a part of your red blood cells. Hb carries oxygen through your body. If you do not have enough iron, your body makes fewer and smaller RBCs. Therefore your body has less Hb, and you cannot get enough oxygen.

Iron is distributed in active metabolic and storage pools. Total body iron is about 3.5 g in healthy men and 2.5 g − in women; the difference is related to women's smaller body size, lower androgen levels, and dearth of stored iron because of iron loss during menses and pregnancy.

The iron in the body of the average man is distributed as follows:

- Hb, 2100 mg;
- ferritin, 700 mg (in cells and plasma);
- hemosiderin, 300 mg (in cells);
- myoglobin, 200 mg;
- tissue (heme and nonheme) enzymes, 150 mg;
- transport-iron compartment, 3 mg.

Iron Absorption

Iron is absorbed in the duodenum and upper jejunum. Absorbtion of iron is determined by the type of iron molecule. Iron absorbtion is the best when food contains heme iron (meat). Dietary nonheme iron must be reduced. Nonheme iron absorption is reduced by other food items (vegetable fiber phytates and polyphenols; tea tannates, including phosphoproteins; bran) and certain antibiotics (tetracycline). Only ascorbic acid is the common food element to increase nonheme iron absorption.

The average American diet, which contains 6 mg of elemental iron/kcal of food, is adequate for iron homeostasis. Adults absorb only 1 mg of iron, which is the approximate amount lost daily by cell desquamation from the skin and intestines from 15 mg/day of dietary iron. Children have a greater need for iron.

Iron Transport and Usage

Iron from intestinal mucosal cells is transferred to transferrin, an iron-transport protein synthesized in the liver; transferrin can transport iron from cells (intestinal, macrophages) to specific receptors on erythroblasts, placental cells, and liver cells.

For synthesis of heme, transferrin transports iron to the erythroblast mitochondria, which insert the iron into protoporphyrin for heme formation.

Transferrin (plasma half-life, 8 days) is extruded for reutilization.

Synthesis of transferrin increases with iron deficiency but decreases with any type of chronic disease.

Iron Storage and Recycling

Iron not used for erythropoiesis is transferred by transferrin, an iron-transporting protein, to the storage pool where it is

stored in 2 forms: ferritin and hemosiderin. The most important is ferritin (a heterogeneous group of proteins surrounding an iron core), which is a soluble and active storage fraction located in the liver (in hepatocytes), bone marrow, and spleen (in macrophages); in RBCs; and in serum.

Iron stored in ferritin is readily available for any body requirement. Circulating (serum) ferritin level parallels the size of the body stores (1 ng/mL=8 mg of iron in the storage pool).

The second storage pool of iron is situated in hemosiderin, which is relatively insoluble and is stored primarily in the liver (in Kupffer cells) and in the marrow (in macrophages).

The body recycles and conserves iron because its absorption is limited. Transferrin grasps and recycles available iron from aging RBCs undergoing phagocytosis by mononuclear phagocytes. This mechanism provides about 97% of the daily iron need (about 25 mg of iron). With aging, iron stores tend to increase because of slow iron elimination.

Etiology

IDA is caused by low levels of iron in the body. Dietary iron barely meets the daily requirement for most people because of poor absorbtion of iron. However, even modest losses, increased requirements, or decreased intake readily produces iron deficiency. Blood loss is almost always the cause, further more it is usually chronic occult bleeding, from the GI tract (this bleeding may be caused by such problems as ulcers, hemorrhoids, or cancer; this bleeding can also happen with regular aspirin use); heavy menstrual bleeding, premenopausal period in women. Bleeding inside the body is the most common cause of iron deficiency anemia in men and postmenopausal women.

Deficiency of vitamin C can contribute to iron deficiency anemia by producing capillary fragility, hemolysis, and bleeding.

Iron requirement is increased (during adolescence, when rapid growth requires a large iron intake; during pregnancy; lactation).

Decreased iron absorption can be the result of gastrectomy and malabsorption syndromes of upper small-intestine. Rarely, absorption is decreased by dietary deprivation from undernutrition, when patients do not get enough iron from food. It can happen in people who need a lot of iron: children from birth to age 2, during adolescence, and pregnant women.

Symptoms and Signs

Mild IDA may not cause the noticeable symptoms. Most symptoms of iron deficiency are due to anemia. Such symptoms include fatigue, loss of stamina, shortness of breath during exercise, weakness, dizziness, irritability, impaired concentration, headache and pallor. Symptoms of severe deficiency include an abnormal craving for eating substances that are not food (pica), in particular, ice, dirt, or paint. Glossitis, cheilosis, concave nails (koilonychia), and, rarely, dysphagia are caused by a postcricoid esophageal web (Plummer-Vinson syndrome). Other signs may include rapid heartbeat; brittle fingernails; cracked lips; smooth, sore tongue; muscle pain during exercise; and difficulty swallowing.

Babies and young children with IDA may not grow as expected and may have delays in skills such as walking and talking. Children may be fussy, irritable and have a short attention span. These problems are usually gone away when deficiency is treated. If it is not treated, mental and behavioral problems will become permanent.

Diagnosis

RBC, serum iron and iron-binding capacity test, serum ferritin test (rarely), and bone marrow examination

Normal serum iron level ranges from 75 to 150 μg/dL (13−27 μmol/L) for men and from 60 to 140 μg/dL

(11−25 μmol/L) for women; total iron-binding capacity is 250−450 μg/dL (45 − 81 μmol/L).

Serum transferrin receptor levels reflect the quantity of RBC precursors available for active proliferation; levels are sensitive and specific. The normal levels are 3.0−8.5 mg/mL. Levels increase in early iron deficiency and with increased erythropoiesis (Table 4).

Serum ferritin levels closely correlate with total body iron stores. Most laboratories range the normal ferritin concentration from 30 to 300 ng/mL, and the mean serrum ferritin concentration is 88 in men and 49 in women. Low levels (<2 ng/mL) are specific for iron deficiency.

Stages of iron deficiency: Laboratory test results help stage iron deficiency anemia (Table 5).

1. Stage 1 is characterized by decreased bone marrow iron stores. Hb and serum iron remain normal, but serum ferritin level falls to <20 ng/mL. The compensatory increase of iron absorption causes the increase of iron-binding capacity (transferrin level).
2. During stage 2, erythropoiesis is impaired. Although the transferrin level is increased, the serum iron level decreases; transferrin saturation decreases. Erythropoiesis is impaired when serum iron falls to <50 μg/dL (<9 μmol/L) and transferrin saturation – to <16%. The serum ferritin receptor level rises (>8.5 mg/L).
3. During stage 3, anemia with normal-appearing RBCs and indices develops.
4. During stage 4, microcytosis and hypochromia develops.
5. During stage 5, iron deficiency affects tissues; symptoms and signs of IDA.

Table 4 − **Differential diagnosis of microcytic anemia due to decreased RBC production**

Diagnostics Criteria	**Iron Deficiency**	**Iron-Transport Deficiency**	**Sideroblastic Iron Utilizatin**	**Iron Reuti-lization**
Peripheral smear				
Microcytosis (M) vs hypochromia (H)	M > H	M > H	M > H , may be normocytic	M > H
Polychromatophilic targeted cells	Absent	Absent	Present	Absent
Stippled RBCs	Absent	Absent	Present	Absent
RBCs				
RBC distribution width	↑	↑	↑	Normal
Serum iron				
Serum iron: iron-binding capacity	↓:↑	↓:↑	↑:Normal	↓:↑
% Saturation of transferrin	< 10	0	> 50	> 10
Serum ferritin				
Normal 30–300 ng/mL)	< 12	No data available	> 400	30–400
Bone marrow				
RBC: granulocyte ratio (normal, 1:3–1:5)	1:1–1:2	1:1–1:2	1:1–5:1	1:1–1:2
Marrow iron	Absent	Present	↑	Present
Ringed sideroblasts	Absent	Absent	Present	Absent

Table 5 − **Differential diagnosis of hypochromic anemias**

Etiology or Type	Morphologic Changes	Special Features
Blood loss, acute	Normocytic normochromic, with polychromatophilia; hyperplastic marrow	If severe, possible nucleated; RBCs and left shift of white blood cells (WBCs); leukocytosis; thrombocytosis
Blood loss, chronic	Same as iron deficiency	Same as iron deficiency
Iron deficiency	Microcytic, with anisocytosis and poikilocytosis; reticulocytopenia; hyperplastic marrow, with delayed hemoglobination	Possible achlorhydria, smooth tongue, and spoon nails; absent stainable marrow iron; low serum iron; increased total iron-binding capacity; low serum and RBC ferritin
Marrow failure	Normochromic-normocytic (may be macrocytic); reticulocytopenia; failed bone marrow aspiration (often) or evident hypoplasia of erythroid series or all elements	Idiopathic (> 50%) but secondary to exposure to drugs or toxic chemicals (chloramphenicol, quinacrine, hydantoins, insecticides)
Bone marrow replacement (myelophthisis)	Anisocytosis and poikilocytosis; nucleated RBCs; early granulocyte precursors; bone marrow aspiration may fail or may show leukemia, myeloma, or metastatic cells	Bone marrow infiltration with infectious granulomas, tumors, fibrosis, or lipid histiocytosis; possible hepatomegaly and splenomegaly; possible bony changes; radioiron uptake greater over spleen and liver than over sacrum

Table 5 (cont.)

Etiology or Type	Morphologic Changes	Special Features
Thalassemia	Microcytic; thin cells; target cells; basophilic stippling; anisocytosis and poikilocytosis; nucleated RBCs in homozygotes	Decreased RBC fragility; elevated Hb A2 and Hb F (often); mediterranean ancestry (common); anemic homozygotes from infancy; splenomegaly; bone changes on X-ray
Sideroblastic anemia	Usually hypochromic but dimorphic with normocytes and macrocytes; hyperplastic marrow, with delayed hemoglobination; ringed sideroblasts	Inborn or acquired metabolic defect; stainable biopsy in bone marrow (plentiful); response to vitamin B6 administration (rare); may be a part of myelodysplastic syndrome

Treatment

Patients will benefit from iron pills if they take them with vitamin C or drink orange juice. Do not take your iron pills with milk, caffeine, high-fiber foods, or antacids. Patients with IDA should take oral supplemental iron and parenteral iron rarely. Iron therapy without pursuit of the cause is a poor practice; the bleeding site should be sought out even in cases of mild anemia. Iron can be provided by various iron salts (ferrous sulfate, ferrous gluconate, ferrous fumarate) or saccharated iron po 30 min before meals (food or antacids may reduce absorption).

A typical initial dose is 100 mg of elemental iron (similar to 325 mg of ferrous sulfate) given 1 or 2 times/day. Parenteral

iron causes the same therapeutic response as oral iron but can cause such adverse effects as anaphylactoid reactions, serum sickness, thrombophlebitis, and pain. It is reserved for patients who do not tolerate or do not take oral iron, or for patients who steadily lose large amounts of blood because of capillary or vascular disorders (hereditary hemorrhagic telangiectasia). The dose of parenteral iron is determined by a hematologist. Oral or parenteral iron therapy should continue for ≥ 6 months after correction of Hb levels to replenish tissue stores.

The response to treatment is assessed by serial Hb measurements until normal RBC values are achieved. Hb rises little for 2 week but then rises 0.7 to 1 g/wk until near normal, at which time rate of increase tapers. Anemia should be corrected during 2 months. A subnormal response suggests continued hemorrhage, underlying infection or cancer, insufficient iron intake, or, very rarely, malabsorption of oral iron.

Patients should not take iron pills: within 2 hours of taking antacids or tetracycline (an antibiotic); with certain foods, chemicals, and nutrients such as tea, coffee, chocolate, and other foods or beverages high in caffeine; milk and other calcium-rich foods or supplements; high-fiber foods such as bran, whole grains, nuts, and raw green vegetables.

For some people, iron supplements can cause stomach discomfort, nausea, diarrhea, constipation, and black (tar) colored stool. Iron is absorbed the best if taken on an empty stomach. But if patients have stomach problems, they may need to take the pills with food.

Prevention of IDA

A patient can prevent anemia by eating foods that include good sourses of iron every day. Iron-rich products include meats, vegetables, and whole grains such as iron-fortified cereals. In order to prevent IDA in babies and children, they

should be fed by certain food for infants, parents should ensure that children reseive sufficient amounts of iron with food. IDA in pregnant women may be prevented by taking prenatal vitamins. A doctor should prescribe prenatal vitamins with iron for pregnant women. A doctor should also test women's blood to see if she has an anemia dignosis. If she has IDA, she will take a higher-dose iron pills. The drug regime depends on the seriousness of anemia.

A diet plan №15 with high levels of proteins, vitamins, iron and microelements is prescribed for iron-deficient patients.

The causal therapy for IDA is radical. It is necessary to eliminate the cause of IDA: to treate enteritis, to do surgery for fibromioma, intestinal tumors and others.

The pathogenetic therapy is prescribed for patients with difficult-to-treate basic deseases.

There are some rules for successful treatment of IDA and latent iron deficiency. The diet is expedient, but it is not enough for full elimination of iron deficiency. The consumption of half-baked liver may be is the cause of salmonellosis and intestinal worms. Eating too much carrot may cause carotene jaundice. Meat products, especially beef, are the most important food sourses of heme iron (Fe+2) that is readily absorbed by the body. There is non-heme iron (Fe+3) in products of plant origin. The absorption of non-heme iron from plant foods is insufficient. Non-heme iron (Fe+3) needs an acidic component to help convert it to heme form (Fe+2) to be easily absorbed.

Blood transfusion is prescribed only for patients with vital indications (Hb<30 g/l, hemodynamic disorders, urgent birth, surgeries). There is a danger of contracting serum hepatitis, inflectional mononucleosis, venereal diseases, and acquired immunodeficiency syndrome.

Such medications as Aktiferrin, Ferrogradument, Heferol, Conferon, Sorbifer Durules, Ranferon-12, Tardyferon are the

main drugs for iron replacement therapy in IDA. The prescription of vitamin B12 and folic acid without special indication is not recommended.

Oral iron supplements are used par excellence. The medicines with iron should be taken before a meal for better absorption. Meat products, especially beef, are the most important food sourses of heme iron (Fe+2) that is readily absorbed by the body.

There are a lot of adverse effects after parenteral introduction of medicines (e.g., Ferrum Lek), such as allergic reactions, anaphylactic shock, phlebitis, infiltration, abscess, siderosis of internal organs, sarcoma of soft tissues. Parenteral iron administration is prescribed according to such indications as poor iron absorbtion, gastrectomy, enteritis with malabsorption syndrome, bowel resection, ineffective primary treatment, or acute ulcer disease.

It is neseccary to continue therapy with iron medicines during the next few months after normalization of hemoglobin and erythrocyte levels to replenish iron stores. Doses and duration of treatment are individual.

There are some stages for IDA treatment.

The first step is the normalization of glycated hemoglobin levels in the blood. It is necessary to prescribe medicines with iron in terms of recovered iron (Fe+2) during 1−2 months. The daily dose is 200−300 mg. For example, we can prescribe 1 tablet of Tardyferon (contains 100 mg of Fe+2) 2 or 3 times a day considering the seriousness of anemia.

The second step is the normalization of iron reserves in the body. Iron medication is prescribed in a half treatment dose (1 tablet of Tardyferon once a day) to be taken during 1−2 months.

The third step is the preventive prescribtion of iron medicines in full treatment dose during one week every month for patients with bleeding or a suspicion of it: women with long

(more than 5 days) and excessive menses, patients with chronic deseases and bleeding, severy diseases, such as unspecific ulcer colitis, diverticulitis, hemorrhoids and others.

Higher doses of iron can cause stomach and intestinal problems, liver failure, dangerously low blood pressure and death. This is connected with the ability of Fe+3 to dissociate and excrete iron ions. Iron ions can denature proteins of mucous membrane. This process results in discomfort, nausea, diarrhea, and constipation**.** Iron binds to hydrogen sulfide that may cause rapid peristalsis or constipation.

The independent iron radicals can enhance the process of lipid peroxidation which is characteristic of the hypoxic state, including antioxidants to prevent reactions with independent radicals.

Introduction of such antioxidants and stimulators of absorption as vitamin E, ascorbic acid, glucose, fruktozodyfosfat, succinic or citric acid is necessary for portability improvement of iron medicine.

The portability of medicines is individual in clinical practice. The selection of optimal medicines according to the portability is empirical.

The positive effect is achieved by the increase of Hb concentration per 1 g/l, in general, during one day (20 g/l during 3 weeks). The greatest increase occurs in severe anemia. The earliest signs of positive treatment effect appear with a higher reticulocyte count (the increase of reticulocyte count quantity on the 4−7 day after the first intake of iron-containing drug, compared to initial count, 2−10 times).

1.2. VITAMIN B12 DEFICIENCY ANEMIA

Deficiency of vitamin B12 causes megaloblastic anemia, damage to the white matter of the spinal cord and brain, and peripheral neuropathy.

Diagnosis is usually made by measuring the level of vitamin B12 in serum.

The Schilling test is used to determine whether body absorbs vitamin B12 normally. Treatment of anemia consists of oral or parenteral introduction of vitamin B12 (Table 6).

Table 6 – **Causes of vitamin B12 deficiency**

Cause	Source
Inadequate diet	- Vegan diet; - Breastfeeding of infants by vegan mothers; - Fad diets
Impaired absorption	- Lack of intrinsic factor (due to pernicious anemia, destruction of gastric mucosa, gastric surgery, or gastric bypass surgery); - Intrinsic factor inhibition; - Decreased acid secretion; - Small-bowel disorders (inflammatory bowel disease, sprue, cancer, biliary or pancreatic disorders); - Competition for vitamin B12 (in fish tapeworm infestation or blind loop syndrome); - acquired immune deficiency syndrome
Inadequate utilization	- Enzyme deficiencies - Liver disorders - Transport protein abnormality
Drugs	- Antacids; - Metformin; - Nitrous oxide

Pathophysiology

Cobalamin is a general form of a compound for biological activity of vitamin B12. This compound is involved into metabolism of every cell of the human body: nucleic acid degradation, methyl compounds transfer, myelin synthesis and maintenance. They are necessary for the formation of normal RBCs. Food-bound vitamin B12 is released in the stomach's acid environment and is bound to R protein (haptocorrin).

Pancreatic enzymes cleave this B12 complex (B12-R protein) in the small intestine. After cleavage, intrinsic factor, secreted by parietal cells in the gastric mucosa, binds with vitamin B12. Intrinsic factor is required for absorption of vitamin B12, which takes place in the terminal ileum. Vitamin B12 in plasma is bound to transcobalamins I and II. Transcobalamin II is responsible for delivering vitamin B12 to the tissues. The liver stores large amounts of vitamin B12. Enterohepatic reabsorption helps to retain vitamin B12. Liver vitamin B12 stores can normally sustain physiologic needs for 3 to 5 years if B12 intake stops (in people who become vegans) and for months to 1 year if enterohepatic reabsorption capacity is absent. B12 is required by enzymes for two reactions: the conversion of methylmalonyl-CoA to succinyl-CoA and the conversion of homocysteine to methionine. In the second reaction, the methyl group of 5-methyltetrahydrofolate is transferred into homocysteine for production of tetrahydrofolate and methionine. This reaction is catalysed by enzyme methionine synthase of B12 as an essential cofactor. During B12 deficiency, this reaction cannot proceed, which leads to the accumulation of 5-methyltetrahydrofolate. This accumulation depletes the other types of folate that are required for purine and thymidylate synthesis, which are required for the synthesis of deoxyribonucleic acid (DNA). As a result of inhibition of DNA synthesis in RBCs, there is the formation of large, fragile megaloblastic erythrocytes. The neurological

aspects of the disease are thought to arise from the accumulation of methylmalonyl-CoA due to the requirement of B12 as a cofactor of the enzyme methylmalonyl-CoA mutase.

Pernicious Anemia

Pernicious anemia (PA) (also known as Biermer's anemia, Addison's anemia, or Addison-Biermer's anemia) is a type of megaloblastic anemia, resulting from vitamin B12 deficiency. Impared intrinsic factor production can occur in adults due to autoimmune destruction of parietal cells, which secret intrinsic factor. Patients with PA, mostly young adults, belong to the increased risk group of gastric and other GI cancers.

SYMPTOMS AND SIGNS OF VITAMIN B12 DEFICIENCY ANEMIA

Vitamin B12 deficiency is usually assosiated with various hematological, gastrointestinal and neuropsychiatric disorders. There are many signs and symptoms that indicate anemia. However, in 20% of cobalamin deficiency cases, anemia is not observed.

Typical symptoms of B12 deficiency anemia:

1. **Anemia:** Anemia may cause fatigue, tachycardia (rapid heartbeat) and cardiac murmurs, along with a yellow waxy pallor, low blood pressure, high blood pressure and shortness of breath (known as "the sighs"). In severe cases, the anemia is able to cause the evidence of congestive heart failure. Other hematological symptoms are cytopenias, intramedullary hemolysis with splenomegaly and hepatomegaly, and pseudothrombotic microangiopathy.
2. **Gastroenterological disorders:** Gastroenterological symptoms may include dyspepsia, nausea, heartburn, diarrhoea, weight loss, and poorly localized neuropathic abdominal pain also may occur. Hunter's glossitis (swollen

red tongue), atrophy of the lingual papillae, and angular cheilitis, usually described as burning of the tongue, are uncommon. Sometimes there appear dehydrated/cracked and pale lips, dark circles around the eyes (look of exhaustion), brittle nails and hair thinning with early greying.

3. **Neurological disorders: They mostly affect white matter of the brain and spinal cord. Demyelinating or axonal peripheral neuropathies can occur.** The symptoms may include difficulties in proprioception (called memory changes), mild cognitive impairment (including difficulty concentrating and sluggish responses, colloquially referred to a brain fog), impaired urination, loss of sensation in the feet, unsteady gait (walking), muscle weakness and clumsiness, and the symptoms of neuropaty. At the first stages, we observe decreased position and vibratory sensations in the extremities, which are accompanied by mild to moderate weakness and hyporeflexia. A complication of severe chronic B12 deficiency anemia results in subacute combined degeneration of spinal cord, which leads to distal sensory loss (posterior column), absent ankle reflex, increased knee reflex response, and the extensor plantar response. The symptoms of the final stages are spasticity, the extensor plantar responses, the greater loss of position and vibratory sensation of the lower extremities, and ataxia.

Diagnosis

Hematological, gastrointestinal and medical disorders: A clinical blood test reveals the symptoms of megaloblastic anemia through a standard complete blood count. The evaluation of the mean corpuscular volume (MCV) as well as the mean corpuscular Hb concentration (MCHC) can help spot hyperchromic anemia.

PA is defined by a high MCV and a normal MCHC (that is, it is a macrocytic, normochromic anemia). Ovalocytes are also typically seen on the blood smear, and a pathognomonic feature of megaloblastic anemias (included PA and others) is hypersegmented neutrophils. **A vitamin B12 deficiency is defined as being vitamin B12 serum levels of under 200 pg/mL (<145 pmol/L).** The Schilling test is used to distinguish PA from other causes of B12 deficiency (intestinal malabsorption**)**. The classic test for PA, the Schilling test, is no longer widely used, as more efficient methods (in addition to the difficulties with radiolabelled agent) are available. The other main diagnostic feature of serum vitamin B12 low levels cannot be relied upon as patients can have high levels of serum vitamin B12 and still have pernicious anemia.

The methylmalonic acid test, performed on blood or urine, is the indication of vitamin B12 deficiency, especially if the B12 deficiency is mild or just beginning. The methylmalonic acid test is often used to clarify ambiguous vitamin B12 test results. The diagnosis of atrophic gastritis type A should be confirmed by gastroscopy and stepwise biopsy. Approximately 90 % of individuals with PA have anti-parietal cell antibodies. However, only 50 % of the population with these antibodies has the PA.

Treatment

- Vitamin B12 1,000 to 2,000 mcg intramuscularly can be given once daily to patients who have severe B12 deficiency or neurologic symptoms or signs.
- Vitamin B12 1,000 mcg intramuscularly is usually given once daily or every other day for several weeks until hematologic values have returned to normal.
- Although hematological abnormalities are usually corrected within 6 weeks (reticulocyte count should have returned to normal within 1 week), but neurologic symptoms may take

much longer treatment. Neurologic symptoms that persist for months or years become irreversible.

For the secondary prevention of Vitamin B12 deficiency anemia, patients should take regular checkups and keep up with cyanocobalamin injections.

1.3. HEMOLYTIC ANEMIAS

Hemolytic anemias (HA) are the group of diseases characterized by increased erythrocytolysis (hemolysis) which occurs if the rate of erythrocyte destruction is increased thereby decreasing erythrocyte lifespan.

The lifespan of erythrocytes in a healthy individual is 100−120 days. Senescent erythrocytes are subjected to sequestering in the spleen, liver and bone marrow. Erythrocytolysis causes the formation of bilirubin yellow pigment in blood as an indirect (unconjugated) bilirubin which is transported to the hepatocytes where it coalesces with glucuronic acid by the enzyme glucuronyltransferase. Bilirubin glucuronide (conjugated) exits the hepatocytes into the bile via the biliary ducts and, together with hepatic bile, it is excreted into the intestine. In case of HA, as a result of intensified erythrocytolysis, the lifespan of erythrocytes decreases to 12−14 days.

1. There are intracellular and intravascular forms of anemia according to mechanism of hemolysis. Intracellular erythrocytolysis takes place in the cells of reticulo-histiocyte system, mainly in the spleen, and it is accompanied by increased content of indirect (unconjugated with glucuronic acid) bilirubin in the blood, increased excretion of urobilin with urine and faeces, and a tendency to stone formation in the gallbladder and the bile ducts. In case of intravascular hemolysis (it takes place in the bloodstream involving complement), hemoglobin in high amounts enters the plasma and excretes with urine in an unchanged form or as

hemosiderin. The latter one can be deposited in the inner organs with subsequent development of hemosiderin.
2. There are two causes of hemolysis, specified by erythrocytic (extracorpuscular) and endo-erythrocytic (corpuscular) factors.
3. There are acute and chronic forms of hemolysis according to the clinical course.
4. All HAs are divided into two big groups called inherited and acquired according to the origin. Hereditary HAs are the result of various genetic defects in the erythrocytes caused by their loss of functional adequacy and endurance.

Hereditary HAs are subdivided into the following pathological forms:
- Membranopathies (Minkowski-Chauffard microsphere-cytosis, ovalocytosis, etc.), associated with erythrocyte membrane disorders caused by changes in erythrocyte shape;
- Enzymopathies caused by deficiency of enzymatic systems in the erythrocytes (G-6-PD, pyruvate kinase, and glutathione reductase);
- Hemoglobinopathies (thalassemia and sickle-cell anemia) caused by failure in Hb structure and synthesis.

Acquired HAs are caused by the following factors which contribute into erythrocytoschisis:
- Action of antibodies (isoimmune, transimmune, heteroimmune and autoimmune);
- Change in the membrane structure of erythrocytes as the result of somatic mutation (Marchiafava-Micheli syndrome);
- Mechanical injury of erythrocyte membranes (valve prosthesis and paroxysmal nocturnal hemoglobinuria);
- Chemical injury to erythrocytes (toxic agents – hydrazine, arsenic, lead, heavy metals, phenol, toluene, benzol, aniline, trichloroethylene, trinitrobenzol, lysol, hydrogen sulphide, acetic acid and other acids, copper, pesticides, etc.);

- Action of biological and bacterial toxins;
- Action of parasites (malaria and toxoplasmosis).

Classifications:

1. According to the International Classification of Diseases, 10th Revision (ICD-10) HAs are assigned the following ICD-10 diagnosis codes: D-55 – anemia due enzyme disorders; D-56 – thalassemia; D-57 – sickle-cell disorders; D-58 – other hereditary HA; D-59 – acquired HA.
2. There is the classification of hemolytic anemia designed by A.I. Vorobiev in 1985:

I. Hereditary HA:

1. Caused by erythrocyte membrane damage:
   a) hereditary microspherocytosis, elliptocytosis, stomatocytosis, and pyropoikilocytosis;
   b) hereditary without Rh- antigens;
   c) structural failure of lipids.
2. Caused by erythrocyte enzyme deficiencies:
   a) deficiency of G-6-PD activity;
   b) erythrocyte pyruvate kinase deficiency.
3. Thalassemias.
4. Caused by disorders of Hb formation:
   a) Hb carriers that change its structure in hypoxia;
   b) sickle-cell disease;
   c) carriers of abnormal stable Hb;
   d) carriers of abnormal unstable Hb.

II. Acquired HA:

1. HA caused by the action of antibodies (immune):
   a) isoimmune;
   b) heteroimmune;
   c) autoimmune.

2. Marchiafava-Micheli syndrome (paroxysmal nocturnal hemoglobinuria).

3. HA caused by mechanical erythrocyte destruction:

a) march hemoglobinuria;
b) mechanical hemolysis following valve and vessel replacement;
c) hemolytic-uremic syndrome (HUS).

4. HA caused by vitamin E deficiency.

The most widespread anemia among hereditary HA is a hereditary microspherocytosis (Minkowski-Shauffard disease). For the first time this disease was described by Minkowski in 1900, and for the second time – by Shauffard with more details. Autosomal-dominant inheritance of the disease is based on the genetic defect of erythrocyte membrane protein or spectrin.

Pathogenesis

As the result of hyperpermeability of defective membrane to sodium ions, there is the increase of water content in the erythrocytes, opposed to biconcave normal ones, that become spherical without deformation when pasing narrow places in the bloodstream. That slows down their movement in the spleen sinuses, partially abrupts erythrocytes with the following formation of microspherocytes (microspherocytosis) and their rapid destruction. Such erythrocytes are absorbed by the macrophage of the spleen. Constant hemolysis of erythrocytes in the spleen causes hyperplasia of splenic pulp cells and an increase of the organ.

Signs and Simptoms

Microspherocytosis has a typical clinical picture of HA with intracellular hemolysis: anemia, jaundice, and spleenomegaly.

Besides, there are such inherent stigmata as skeleton deformation (arched skull, high "Gothic" palate, broad nose bridge, short fingers), eyes and teeth anomaly, and otosclerosis. Anemia usually affects adolescents, sometimes − adults. The severity of anemia depends on erythrocytoschisis rate and recovery properties of erythropoiesis ratio. In young people, anemia causes disorders of mental and physical development. Subjectively, sick people feel considerably better when erythrocytes and Hb indices are lower than in IDA. On the one hand, the intensity of jaundice depends on the degree of erythrocytoschisis, on the other hand − on functional capacity of the liver associated with the ability to combine bilirubin and glucuronic acid and to excrete them together with bile. If hemolysis is not clinically apparent, jaundice may be absent. As the result of jaundice and anemia combination, the skin becomes lemon-colored.

Formation of gallstones is caused by a three-fold increase in bilirubin level in the bile (pleiochromy).

Cholelithiasis with a hepatic colic attack or development of obstructive (mechanical) jaundice is a frequent complication of microspherocytosis. In case of latent clinical course of hemolytic disease without apparent anemia and jaundice but with decreased lifespan of erythrocytes, increased billirubin level in the bile and increased stercobilinogen outflow dominate in the clinical picture. Some time later cholelithiasis may occure with such complications as cholestatic hepatitis and hepatocirrhosis. Splenomegaly in case of microspherocytosis doesn't develop significantly. Against the background of chronic course of hemolytic anemia under the influence of any infection or concussion, hemolytic crisis with sudden deterioration of general state may occure with exacerbation symptoms (increased severity of anemia, jaundice, urobilinuria), and temperature rise.

One of the most dangerous complications of HA with severe clinical course is hypoplastic crisis associated with temporary erythropoiesis insufficiency during 7−15 days. Such patients are in urgent need of medical care.

Laboratory diagnosis includes the following key findings:

- Degree of severity: most frequent is moderate normochromal anemia (Hb and erythrocyte rates decrease simultaneously). After hemolytic crisis anemia intensifies (Hb rates sometimes decrease to 20−30 g/l);
- Erythrocytes look like microspherocytes;
- Reticulocytosis, most frequently moderate, reflects the degree of compensatory hematopoiesis in the bone marrow. It intensifies after hemolytic crisis and is absent after hypoplastic crisis: the number of platelets and leukocytes remains the same, but after the crisis, leukocytosis occurs due to activated neutrophils, accompanied by neutrophic left shift;
- Bilirubinemia at the expense of unconjugated bilirubin, an increase of conjugated one in case of cholelithiasis. Normal rates are possible in case of satisfactory function of the liver and insignificant hemolysis (diagnosis of hemolytic anemia cannot be excluded);
- Urobilinuria (the degree of manifestation also depends on the liver function);
- Increase of stercobilinogen in feces (dark color of feces − pleioschomy);
- Increased iron content in blood serum;
- Myelogram shows signs of hyperplasia of the red blastema with erythronormoblastic reaction: the number of erythrokaryocytes in the bone marrow is more than 25%; in case of hypoplastic crisis erythroblastopenia occurs.
- Osmotic resistance of erythrocytes decreases: the beginning of hemolysis with 0.75% sodium chloride, and the termination

of haemolysis – 0.45% (0.45−0.4 − healthy people and 0.35 − sick people correspondingly).

Diagnosis Criteria

Normochromal anemia, jaundice, splenomegaly, microspherocytes in the peripheral blood, reticulocytosis, reduction of osmotic fragility of erythrocytes, hyperbilirubinemia (with prevalence of unconjugated fraction), urobilinuria, large amount of stercobilin in feces, hyperplasia of erythroid lineage in myelogram (prevalence of erythro- and normoblasts).

Treatment

One of the most effective methods for hereditary microspherocytosis treatment is splenectomy, where spherocytes remain, while the anemic syndrome is suppressed. If there is no effect of splenectomy, it indicates inadequacy of the diagnosis or presence of an accessory spleen. Splenectomy in the pediatric age (in children younger than 10 years) increases the risk of infectious diseases because of inferiority of the immune system.

Direct indications for splenectomy are:

- hemolytic and hypoplastic crises;
- pediatric anemia which can range from stable moderate to severe acute and unstable that negatively affects physical and mental development of children;
- morbid states that are complicated by cholelithiasis with hepatic colic and cholestatic hepatitis (in such cases splenectomy is performed together with cholecyctectomy).

In case of severe hemolytic or hypoplastic crisis, a transfusion of red blood cell concentrate is indicated.

1.3.1. HEREDITARY ENZYMOPATHY (FERMENTOPATHY)

Etiology

HA which is associated with the enzyme defects in glycolysis, pentosephosphate pathway, and glutathione senthetase deficiency is inherited in a recessive manner.

Pathogenesis

HA which is caused by enzyme defects in glycolysis is associated with the disturbance of adenosine triphosphate formation in the erythrocytes.

Ionic composition in such erythrocytes changes, their vital capacity decreases, and they are rapidly destroyed by macrophages in spleen and liver.

Enzymes activity is defected in pentosephosphate path and the glutathione system causes the change of lipids in the membrane which is incapable to resist the action of oxidizing agents. After taking such medication as sulfanilamides or antimalarial drugs, or eating fava beans (favism) such erythrocytes are rapidly destroyed and more often removed from the bloodstream (hemolysis), but intracellular hemolysis is also possible.

Clinical picture

HA with the presence of enzyme defects is able to devide into various degree of severity – from oligosymptomatic to severe forms. Intracellular hemolysis prevails. The spleen is enlarged; in some cases the liver is enlarged too. It is often combined with hereditary anomaly: visual impairment, myasthenia, affection of the nervous system, leukopenia, and thrombocytopenia.

With the presence of defects in the enzyme system of pentosephosphate path, including defects in G-6-PD and

glutathione taking some medicine (quinine, acrichine, sulfonamides, and fava beans cause the development of hemolytic crisis with intravascular hemolysis: hemoglobinuria, hemosiderinuria, sometimes hemorrhagic syndrome as the result of thrombocytopenia and coagulation failure – disseminated intravascular coagulation (DIC) syndrome. Constant intracellular hemolysis occurs quite rarely.

Laboratory Diagnosis

In case of intravascular hemolysis (enzyme deficiencies in the glycolytic pathways), normochromal anemia, reticulocytosis, bilirubinemia, urobilinuria, stercobilin increase in feces, unchanged osmotic resistance of erythrocytes, intensified and corrected by adding glucose autohemolysis, intensified erythropoiesis in the myelogram are observed.

In case of HA with intravascular haemolysis (defects of enzyme activity of pentosephosphate pathway and reduced glutathione production) hemoglobin level increases, and hemosiderosis of internal organs may occur.

Treatment

In most cases, when there is a constant chronic intravascular hemolysis, a partial effect may occur as a result of splenectomy. In case of enzymopathies, which are accompanied by glutathione restoration disturbance, taking flavinat (2mg 2−3 times a day) or riboflavin brings relief.

HA with enzymopathy is incurable. To prevent hemolytic crisis, medications should be taken with caution.

1.3.2. HEREDITARY HEMOLYTIC ANEMIA CAUSED BY ABNORMAL HEMOGLOBIN

DISORDERS OF HEMOGLOBIN SYNTHESIS

This group of diseases includes HA that are associated with disorders in the synthesis rate of one or more polypeptide chains of globin (thalassemia) and HA caused by a change of the primary structure of polypeptide chains which results in stability and function disturbance of Hb (hemoglobinopathy with abnormal Hb).

Hb abnormalities quite often affect inhabitants of the Mediterranean region, Central and East Africa, Middle East, South Asia and South-East Asia, and African Americans. The disease is also spread throughout the Caucasus, Transcaucasia, and Central Asia.

1.3.3. THALASSEMIA

Etiology

Thalassemia is a group of inherited diseases that is characterized by deletion or mutation of genes that control globin production of hemoglobin chains. Most thalassemias are inherited as an autosomal recessive or dominant trait.

Pathogenesis

A globin molecule of a healthy individual consists of 2 pairs of polypeptide chains. Fetal hemoglobin (als. Hb F, hemoglobin F or $\alpha 2\gamma 2$) consists of 2 α-chains and 2 γ-chains. Gradually, Hb F is nearly almost replaced by Hb of an adult – Hb A which is nonhomogeneous and consists of Hb A1 (97 %), that consists of 2 α-chains and 2 β- chains ($\alpha 2\beta 2$), and Hb A2 (3 %), that consists of 2 α-chains and 2 δ-chains ($\alpha 2\delta 2$). Depending on the types of globin chains that are reduced,

specialists distinguish α- and β-thalassemias. More frequent β-thalassemia is characterized by a genetic deficiency in the synthesis of β-globin chains (the reduced β+ or absent β0 synthesis of the β-globin chains of the globin tetramer): this causes the decrease in HbA1 and the increase in Hb F and Hb A2 levels.

Clinical Picture

Thalassemia is a HA that leads to intracellular haemolysis of various forms of severity (from subclinical forms to severe hemolysis).

According to a severity degree, there are thalasemia major (homozygous – Cooley's anemia) and thalassemia minor (heterozygous mediterranean anemia) β-thalassemia.

Signs of thalassemia major may be noticed in the first year of life; especially severe cases cause death. In case of mild HA, the patients can reach their puberty. A mild case of HA is diagnosed in the second year of life, and such patients live till their mature age. The typical symptoms for thalassemia major are paleskin, with some grayish-yellow tinge, growth inhibition and large size of a head (Mongoloid face and square skull as a result of intensified hyperplasia of bone marrow). The children suffer from growth retardation. X-ray examination of cranial bones shows thickening of plates and trabeculal of spongy bones in the form of a brush as a result of intensified hematopoiesis. The abdomen is enlarged because of the liver and spleen enlargement. In case of mild homozygous β-thalassemia, cholelithiasis, hemosiderosis, trophic ulcer, various infections, and circulatory disturbances occur in the background of lingering clinical course of the disease.

Most patients with (heterozygous) β-thalassemia minor have a latent form of the disease and live a full life. Sometimes the disease is diagnosed by accident. In some cases, there is a marked HA with slight icterus and an enlarged spleen. The

signs of HA are more intense in infections or during pregnancy.

Clinical signs of α-thalassemia depend on the number of missing genes. In case of a homozygous major form provided the lack of 4 genes, intrauterine death of the fetus occurs (hydrocephalus and marked hepatosplenomegaly). Patients with heterozygous forms of thalassemia can suffer from moderate to mild HA, yellow coloring of the skin and anemia.

Laboratory diagnosis shows typical symptoms of intracellular hemolysis.

Screening test of thalassemia reviels that osmotic resistance of erythrocytes increases. When thalassemia is suspected, the type of Hb must be defined with the help of electrophoresis on the various carriers. In the uncertain cases, the rate of Hb chain synthesis, including labeled amino acids, should be examined.

Homozygous β-thalassemia is characterized by the absence of HbA1 (β0-thalassemia) or the decrease of its degrees (β+-thalassemia), or increase of HbF and HЬA2 degrees. Heterozygous β-thalassemia is also characterized be moderate increase of HЬ F and HbA_2 degrees. In case of α-thalassemia, a ratio between various types of Hb does not change, but the α-chain synthesis is delayed.

Symptomatic principle is one of the thalassemia treatment principles.

Repeated hemotransfusion is the basic method of treatment for homozygous thalassemia. To avoid sensitizing, first of all, washed or defrosted erythrocytes are used every 2−3 days to elevate Hb level. Then the treatment includes supportive hemotransfusion (every 3−4 weeks) untill Hb level has been increased to 90−100 g/l.

This tactics is especially important in the reatment of children to ensure their better physical and mental development.

We should prescribe desferal to bind free iron in the bloodstream and enhance its elimination in the urine, because iron is not used in treatment of thalassemia but causes susceptibility to hemosiderosis of the internal organs.

Splenectomy should be carried out in marked hypersplenism or in repeated splenic infarctions.

There is no need in hemotransfusions or splenectomy in heterozygous α- and β- thalassemia. Repeated infusions of Desferal are required. Iron preparations are strongly contraindicated. Folic acid is recommended for elevation of erythropoiesis in pregnant women with infections.

1.3.4. HEREDITARY HEMOLYTIC ANEMIA CAUSED BY STRUCTURAL FAILURE IN HEMOGLOBIN CHAINS

This type of anemias includes hereditary HA caused by the presence of abnormal Hb as a result of substitution of one or more amino acids in the polypeptide chain of globin.

Nowadays, more than 150 abnormal Hb are known. Substitution occurs in the β-chain most often.

Etiology

Hereditary diseases occur as a result of dripping mutation in the genes that code the formation of globin chains most often are inherited according to autosomal dominant pattern.

Pathogenesis

Clinical presentations of abnormal Hb depend on the molecular structure and its functional changes. Generally, abnormal Hb are stable in homo- and heterozygote conditions, the pathology is not clinically evident, and abnormal Hb are diagnosed accidentally.

Sometimes, substitution of amino acids causes the change in the configuration of globin chains, their correlation violation and the change in the strength of heme attachment. Such types of hemoglobinopathy have certain clinical manifestations. The most common of them is a sickle-cell anemia or hemoglobinopathy S. In case of this disease, Hb A is substituted by Hb S (sickle-cell hemoglobin) that, in turn, replaces glutamic acid with valine in the β-chain. As a result of partial pressure decrease, conditioned by hypoxia, solubility of Hb S solubility is almost 100 times less compared to normal Hb, its molecules crystallize, erythrocytes elongate and deform, which causes an increase in blood viscosity, and its stasis leads to microthrombosis, ischemia, necrosis, and fibrosis. Defective erythrocytes are rapidly destroyed in the spleen. That's why an enlargement of the spleen is evident even in the early stages of the disease, and repeated splenic infarctions result in autosplenectomy. Furthermore, in the abnormal Hb the heme of iron was oxidized to form methaemoglobin, in which Hb is strongly combined with oxygen, and cyanosis and the development of polycythemia are caused by them.

Clinical Picture

A broad clinical picture in case of homozygous form of sickle cell anemia is revealed from the first six months of a child's life, when fetal Hb has been substituted by Hb S. The clinical picture includes the signs of moderate HA and severe venous thrombosis in internal organs. Typical symptoms of sickle cell anemia such as fatigue, anemia, pain creses, and bone infarcts can occur at any age. Infants and younge children can suffer with fever, abdominal pain, bacterial infections, painfull swelling of the hands and feet, and splenic sequestration. Young adults develop leg ulcers, aseptic necrosis and eye damage. Symptoms in adults typically are intermittent pain episodes due to injury of bones, muscle or internal organs.

There is the ability of development of leg ulcers and priapism sometimes. Physical development and sexual maturation of a child are delayed.

On the other hand, the background of complications (such as bacterial infections and thrombosis) in patients with homozygous patients with sickle cell anemia, quite often a hemolytic crisis with acute intravascular hemolysis, aplastic and hypoplastic crisis, and sequestration crisis (associated with a massive flow of erythrocytes from the blood stream to the internal organs) develop. Heterozygous sickle cell anomaly is characterized by the absence of clinical symptoms that appear only during hypoxia (e.g., pneumonia, narcosis, mountain climbing, or scuba diving).

Laboratory Diagnosis

Besides diagnosis of HA, sickle-cell anemia is characterized by the presence of sickle erythrocytes (meniscocytes). Sickle resemblance becomes evident in the conditions of hypoxia when performing some special tests (with sodium metabisulfite and after application of tourniquet on the finger). The character of hemoglobinopathy can be clarified by performing Hb electrophoresis. In a homozygous form of sickle cell anemia electrophoregram demonstrates the presence of Hb S fraction and absence of of Hb A fraction. The presence of Hb S and Hb A fractions are common to the heterozygous form of (sickle-cell disease).

Differential diagnosis of hemoglobinopathies is performed in case of liver diseases (infectious hepatitis, chronic hepatitis, mechanical jaundice), and other HA of hereditary and immune nature. Sometimes, it is necessary to carry out a differential diagnosis of thrombolytic complications of sickle-cell anemia with corresponding diseases of joints, liver, kidney etc.

Symptomatic treatment of sickle-cell disease includes:
- hemotransfusion, performed in severe forms of the disease (transfusion of washed erythrocytes, or packed RBCs);
- oxygenotherapy and hemodilution by alkaline saline solutions to reduce the number of sickled cells;
- splenectomy in patients with hypersplenism;
- anesthetics, sedatives, spasmolytics, hydration by saline solutions are indicated in vaso-occlusive;
- anti-infective therapy, especially in pulmonry infections, since hypoxia increases the manifestation of the disease;
- folic acid is indicated because of intensified ineffective hemopoiesis;
- desferal – the medicine for preventive treatment of hemosiderosis.

1.3.5. IMMUNE HEMOLYTIC ANEMIA

Immune HA is a group of diseases that are caused by immune disorders (antibodies, antigen-primed lymphocytes) which is resulting from destruction of erythrocytes of a patient.

There are 4 types of immune processes, depending on their nature:
- Isoimmune HA which is caused by isoantibodies or autoantibodies produced on exposure to drugs, toxins or other antigens. Antibodies enter the body from the outside (hemolytic disease of a fetus or a newborn), or erythrocytes, against which there are isoantibodies in the patient's body (with incompatible blood transfusion);
- Transimmune HA, when anti-erythrocyte antibodies or a mother who sufferes from immune HA, are passively transported through the placenta and cause HA in the baby;
- Heteroimmune HA types are caused either by antibodies against modified exogenous factors (medicines) of erythrocyte antigens (haptenic hemolytic anemia), or by antibodies against

external agents (bacteria, viruses), which react with erythrocyte antigens; or erythrocytes are nonspecifically injured by exhausted immune complexes.
- Autoimmune hemolytic anemia (AIHA) is associated with the production of antibodies directed against there own unchanged erythrocyte antigens.

1.3.6. AUTOIMMUNE HEMOLYTIC ANEMIA

According to serologic diagnosis, we differentiate 4 types of autoantibodies and forms of AIHA, which have the following peculiarities of the clinical course:

- AIHA with incomplete thermal aglutinamines;
- warm AIHA (caused mainly by warm-reactive Ig G-mediated extravascular hemolysis);
- cold AIHA (usually due to complement-mediated intravascular hemolysis);
- mixed type AIHA (based on the termal range of autoantibodies involved in the pathogenesis).

AIHA may appear without any reason (idiopathic AIHA) or as a complication of another disease (symptomatic AIHA). Symptomatic forms of AIHA are observed in hemoblastosis, especially in lymphoprofilirative diseases, autoimmune diseases (colagenosis, nonspecific ulcerative colitis, chronic hepatitis etc.), malignant tumors, primary (hereditary) immunodeficiency and with the uses of α-methyldopa.

Etiology

AIHA is a process which is associated with the loss of immunological tolerance to native antigens as a result of primary changes in the immunocompetent system (proliferation of genetically changed lymphoid cells, deficiency and reduced T cell suppressor functions, appearance of cross-reacting antibodies, etc.).

Pathogenesis

AIHA is defined by the nature of antibodies. Incomplete thermal (warm) agglutinins bind to erythrocytes, changing permeability of the membrane for sodium ions. Spherocytosis with subsequent elimination of erythrocytes develops in the spleen. Intracellular hemolysis mechanism prevails. Thermal hemolysins, two-phase cold hemolysins and complete cold agglutinins cause destruction of erythrocytes in the bloodstream with intravascular haemolysis.

Clinical Picture and Diagnosis of AIHA with Incomplete Thermal Hemolysins

The course of the disease is quite variable, starting with subclinical forms (with gradual onset without subjective signs and anemia) and ending with acute hemolytic crisis and progressive shock.

AIHA with subacute course provoked by old infections is the most common form. The temperature rises, joints and stomach are painful, the signs of anemia are accumulating (dizziness, abnormal pale, rapid or irregular heartbeats, and tachycardia).

There are some clinical signs of HA with intracellular hemolysis that are defined by corresponding laboratory changes. Sometimes AIHA is accompanied by autoimmune thrombocytopenia (Fisher-Evans syndrome).

Serological examination shows positive direct Coombs test, which helps to find incomplete thermal agglutinins, fixed on the surface of erythrocytes, but with insufficient number of antibodies, the test can be negative: this does not exclude the disagnosis of AIHA. Other immunologic disorders are possible (the level of immunoglobulin changes; there appear anti-nuclear, anti-immunoglobulin, and antilymphocytic antibodies, rheumatoid factor, and false-positive syphilis reactions).

Clinical Picture and Diagnosis of Warm AIHA

This form of HA is rarely observed. Clinical periods of exacerbation (with intravascular mechanism of hemolysis) alternate periods of remission. Hemolytic crisis is characterized by hyperhemoglobinemia and hemoglobinuria (dark urine, sometimes black), and hemosiderinuria. Thrombotic complications develop quite often. This form of AIHA is conditioned by the presence of thermal acid hemolysins that are fixed on the surface of erythrocytes and cause hemolysis if there is a complement. Antibodies are detected with the help of indirect Coombs test with erythrocytes treated by papain.

Clinical Picture and Diagnosis of Cold AIHA (Cold Agglutinin Disease)

Clinical manifestations of the disease are peripheral bloodstream disorders with signs of intravascular hemolysis caused by hypothermia. Peripheral disorders of a bloodstream (acrocyanosis of ears, nose, and fingers, Raynaud's syndrome; thrombosis and gangrene of fingers; and cold urticaria) are the result of erythrocyte agglutination in the capillaries in low body temperature. It ceases quickly in warm conditions. Usually hemolysis is not quite evident, and it is accompanied by hemoglobinemia. Only continuous overcooling provokes the crisis of hemoglobinuria. First signs of cold AIHA are observed when there are some difficulties in preparing peripheral blood smear, calculating blood corpuscle and determining blood group, because of autoagglutination of erythrocytes at room temperature. Therefore, it is possible to receive the results only when performing the investigation at 37 ºC. A blood group of such paients is determined after washing erythrocytes with warm isotonic sodium chloride solution. In serological studies, complete cold agglutinins in a high titre are determined with the help of indirect Coombs test

and acid cold hemolysins which cause agglutination and haemolysis of erythrocytes in the presence of complement.

Clinical Picture and Diagnosis of Cold AIHA Biphasic Hemolysin (Paroxysmal Cold Hemoglobinuria)

The onset of the disease is acute: as the result of hypothermia, acute hemolytic crisis with hemoglobinuria starts, sometimes accompanied by Raynaud`s syndrome or urticarial vasculitis. Hemolysis lasts 2−3 days, that is why anemia is not long-lasting. Intravascular hemolysis can be caused by overcooling of the feet and hands in icy water.

Serological investigation confirms the presence of biphasic cold hemolysins, also called Donath-Landsteiner hemolisins, which bind to RBCs only at cold temperatures and cause complement mediated hemolysis only after warming to body temperature.

Differential Diagnosis of AIHA should be performed in liver diseases with jaundice, kidney diseases, and different anemias – dyserythropoietic and megaloblastic anemias, accompanied by hemolysis of erythrocytes, hereditary HA, and Marchiafava-Micheli disease. Sometimes, there are some difficulties in differential diagnosis of idiopathic and secondary AIHA, especially if the underlying disease is considered a latent disease, and clinical signs of AIHA prevail. In some cases AIHA has been the first manifestation of the underlying disease for several years, and it is considered an idiopathic autoimmune anemia.

Treatment

The main treatment principle of AIHA is the prescription of glucocorticoids (prednisolone and its analogues) in large doses (first, 0.6−1 mg/kg per day during 2 weeks, and if there is no positive effect – 1.5−2 mg/kg). The dosage is gradually

reduced to a maintenance dose, under the control of a blood test.

The smaller the dose is, the slower is the rate of lowering the dosage. A large dose is 5 mg per day, starting with 30 mg: 2.5 mg during 4−5 days, then 2.5 mg during 2 weeks.

Only 2.3% of patients treated with prednisolone show complete remission with normalization of blood values and negative markers of autoimmune hemolysis; 28% of patients achieve complete remission, but their immunological tests are positive; and 50% of patients have only temporary effect from treatment with prednisolone while a decrease in the dose or its elimination cause a relapse of the disease. That is why more than half of the patients need a maintenance dose of prednisolone (5−15 mg/day) for a long period of time.

In conclusion, it is difficult for patients with AIHA to tolerate hemotransfusion; therefore, it is performed only in case of severe exacerbation – acute hemolytic crisis with possible shock development and severe anemia.

Washed or defrosted erythrocytes should be chosen individually, with previously performed negative Coombs test. Patients with AIHAs with incomplete thermo hemolysin and prevalent intracellular hemolysis require a splenectomy. Young people, who are regularly taking a maintenance dose of prednisolone or have quite short remissions, need splenectomy first of all. There is a positive effect after surgical operation in 60% of cases. A decrease in the frequency of crises and in prednisolone doses after operation is observed in 20% of patients.

If there is no positive effect or there are contraindications to glucocorticoids and splenectomy, the doctor prescribes immune inhibitory therapy with 6-mercaptopurine (150−200 mg per day), Imuran (200−250 mg per day) or Cyclophosphan (400 mg per day) to reach remission with subsequent maintenance therapy with smaller doses. It is not

appropriate to indicate immune inhibitory therapy to children during haemolytic crisis.

The treatment of AIHA with the help of cold antibodies has some peculiarities. Corticosteroids are less effective and should be prescribed in small doses (15−25 mg per day). Cyclophosphan or chlorbutin (2.5−5 mg per day) are more preferable medications among immune inhibitors. Splenectomy is not effective. Therapeutic plasmapheresis is recommended (at temperature 37 ºC).

Symptomatic AIHAs in most cases are cured by treatment of a basic disease or by achieving a complete remission.

To prevent a hemolytic crisis in case of cold AIHA an overcooling is contraindicated.

1.3.7. ACQUIRED HEMOLYTIC ANEMIA WITH PREVALENT INTRAVASCULAR HEMOLYSIS

Etiology

Transfusion of incompatible blood, hemolytic toxicity, snake venom poisoning, malaria, Marchiafava-Micheli disease, and march hemoglobinuria are main causes of HA with intravascular mechanism of hemolysis. Some medicines acetic acid, or septic abortions provoke an acute hemolytic crisis.

Clinical picture depends: on the rate and intensity of hemolysis, the causes of hemolysis and anemia severity.

Main symptoms of hemolytic crisis are rapidly developed weakness, increased body temperature, dyspnea, intensive headache and low back pain, stomach ache, nausea, bile vomiting, and sometimes purgative defecation (dark-colored stool). The patient’s condition is serious, and tachycardia is evident. The skin is yellow, like a lemon, visible mucous membranes are pale. Specific sign of crisis is black or maroon colour of urine (hemoglobinuria). Sometimes oliguria and anuria with probable subsequent development of acute renal

insufficiency may occur. Sometimes hemorrhagic syndrome with appearance of typical skin rash – atomized petechial and small fruises, bleeding sickness of mucous membranes can be observed. Coagulation and hemostasis defects and acute renal insufficiency are caused by development of DIC, which is the result of abnormal exposure of blood to tissue thromboplastin or tissue factor. Tissue factor is released from the surfaces of cells during lysis of fibrin clots. Moderate hemolysis is not accompanied by acute renal insufficiency. In mild cases of intravascular haemolysis, it is accompanied by mild jaundice and insignificantly dark urine.

Laboratory Diagnosis

Beside typical changes that characterise HA with intravascular hemolysis, there are some changes in the blood coagulation system. Blood coagulation rates depend on acuteness and intensity of the hemolytic crisis and the acquisition time. At the beginning of hemolytic crisis there is a clear blood hypercoagulation. Then the phase of hypercoagulation changes to the phase of hypocoagulation with typical for DIC changes.

Treatment

In hemolytic crisis, during acute intravascular hemolysis, heparin (5.000 units intravenously) is prescribed, and then the introduction continues drop-by-drop (25 u/kg/hr, about 40.000 units per day). The dose should be selected according to the control of prothrombin time and autocoagulation test (the prothrombin time must be increased twice). Rheopolyglucin and steroid hormones are introduced. Plasmapheresis procedure should be conducted over a fixed time period. It involves 500−1000 mg of removing plasma and substituting by fresh frozen plasma and blood substitutes. If required plasmapheresis is conducted daily; in case of acute renal

failure, Prostenonum is introduced (2−5 mg in 300 ml of isotonic solution of sodium chloride, intravenous, drop-by-drop, once a day). It must be repeated during 3−5 days. If there is no effect, hemodialysis is performed. In case of clinically apparent anemia, transfusion of washed RBCs with heparin content is indicated.

1.3.8. HEMOLYTIC ANEMIA ASSOCIATED WITH MECHANICAL DAMAGE TO THE ERYTHROCYTE MEMBRANE

The mechanical ingury to the erythrocyte membrane may be associated with prosthetic cardiac valve or membrane. The mechanical injury to erythrocytes may be caused by the surface of the prosthesis or by increased lysis in the vortices that are formed after prosthetics.

HA can occur on the first day or a few days or weeks after surgery. The intensity of hemolysis varies within a fairy wide range. A moderate degree of intravascular hemolysis after surgery is rather common. Quite typical are morphological changes in erythrocytes − fragmented erythrocytes appear as schistocytes, often triangular, or keratocytes, i.e. helmet shaped. In some cases AIHA can occur as a result of sensitization of the human body by antigens of damaged erythrocytes. Hemolysis stops after elimination of the cause of the hemolysis (sometimes, after reoperation).

March hemoglobinuria is a rare abnormal condition typical for healthy people (soldiers, athletes) after long running, protracted marching or heavy physical exercises. It is caused by repeated mechanical injury to erythrocytes in the vessels of hands and feet. It is assumed that close location of the capillaries to the surface of the foot matters. Clinical picture shows prevalence of moderate intravascular HA. Hemoglobinuria can be observed during some hours, but later

on it completely vanishes and can be indused throught repetitive mechanical motion. The patient's general condition is not violated: sometimes the patients feel moderate weakness, burning sensation in the heels and discomfort in the lower back. The temperature does not rise. Acute renal insufficiency is not typical. It is detected occasionally; it is benign. Such patients do not need treatment.

Examples of diagnostic framing:

1. HA: congenital sickle-cell disease with hemolytic crisis.
2. HA: microspherocytic (Minkowski-Chauffard) anemia with hemolytic crisis.
3. HA: autoimmune disease with incomplete warm agglutinin and hemolytic crisis.
4. Paroxysmal hemoglobinuria (Marchiafava-Micheli disease) with hemolytic crisis.

1.4. APLASTIC ANEMIA

Aplastic anemia is a normocytic-normochromic anemia resulted from a loss of blood cell precursors, causing hypoplasia of the bone marrow, RBCs, WBCs, and platelets. Symptoms result from severe anemia, thrombocytopenia (petechiae, bleeding), or leukopenia (infections). To make a diagnosis it is necessary to identify peripheral pancytopenia and the absence of cell precursors in the bone marrow. Equine antithymocyte globulin and cyclosporine are used in treatment. Recombinant human erythropoietin and granulocyte-macrophage colony-stimulating factor, and allogenic bone marrow transplantation may improve anemia.

The term "aplastic anemia" usually implies a panhypoplasia of the bone marrow with associated leukopenia and thrombocytopenia. Selective hypoplasia of erythroid elements

is termed pure RBC aplasia. Despite the fact that both disorders are rare, aplastic anemia still occurs more often.

Etiology

True aplastic anemia (most common among adolescents and young adults) is idiopathic in about half of the cases. Recognized causes of aplastic anemia are chemicals (e.g, benzene and inorganic arsenic), radiation, and drugs (e.g, antineoplastic drugs, antibiotics, Nonsteroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, acetazolamide, gold salts, penicillamine, quinacrine). Mechanism of action is unknown, but selective (perhaps genetic) hypersensitivity turned out to be the principal.

Fanconi`s anemia is a very rare inherited blood disorder that leads to the bone marrow failure (aplastic anemia), microcephaly, hypogonadism, and brown pigmentation of skin. It is occured among children with chromosome abnormalities. Fanconi`s anemia is sometimes inapparent until there is some disease (especially an acute infection or inflammatory disorder) that causes peripheral cytopenias.

Pure RBC aplasia may be acute and reversible. Acute erythroblastopenia is a brief disappearance of RBC precursors from the marrow in different acute viral infections (particularly, human parvovirus infection (B19V)), especially in children. The duration of anemia is longer than that of acute infection.

Chronic pure RBC aplasia is associated with hemolytic disorders, thymomas, autoimmune mechanisms and sometimes with drugs (e.g., tranquilizers, anticonvulsants), toxins (organic phosphates), riboflavin deficiency, and chronic lymphocytic leukemia. A rare congenital form, called Diamond-Blackfan anemia, usually occurs in infants but has been also reported in adults. Diamond-Blackfan anemia is associated with structural abnormalities such as small head size, characteristic facial

features, cleft palate, cleft lip, defects of the hands (mostly of the thumbs), as well as defects of the genetalia, urinary tract, eyes and heart. Sometimes, there is also short stature.

Symptoms and Signs

Although the onset of aplastic anemia is usually insidious, it can manifest itself over weeks or months after exposure to a toxin. Sometimes the disease is acute. Signs vary depending on the severity of pancytopenia. Symptoms and signs of anemia such as pale skin, petechiae, ecchymosis, and bleedings from the gums, into the conjunctivae, or in other tissues are caused by severe thrombocytopenia.

Agranulocytosis makes people more vulnerable to picking up life-threatening infections. Splenomegaly is absent unless induced by transfusion hemosiderosis. Symptoms of pure RBC aplasia are usually mild and depend on the degree of anemia or underlying disorder.

Diagnosis

- anemic syndrome;
- infectional syndrome;
- hemorrhagic syndrome;
- complete blood count (CBC);
- bone marrow examination.

Aplastic anemia is most common in young patients, especially in those with pancytopenia (e.g., WBC <1,500/μL, platelets <50,000/μL). Pure RBC aplasia (including Diamond-Blackfan anemia) is suspected in patients with bony abnormalities and normocytic anemia but normal WBC and platelet counts. If either diagnosis is suspected, bone marrow examination is done.

Aplastic anemia is characterized by normochromic normocytic (sometimes marginally macrocytic) RBCs. Reduction in the WBC count occurs chiefly in the

granulocytes. A platelet count is often less than 50,000/μL. Reticulocytes decrease in number or are absent. Serum iron is elevated. Aplastic anemia is characterized by acellular bone marrow. Normocytic anemia, reticulocytopenia, and elevated serum iron are the characteristic of pure RBC aplasia, but the levels of WBC and platelet counts are normal. Bone marrow cellularity and maturation can be normal except the conditions when erythroid precursors are absent.

Treatment

Equine antithymocyte globulin, corticosteroids, and cyclosporine are medicines for aplastic anemia treatment. Sometimes hematopoietic cell transplantation, cytokines, and surgery for thymoma are associated with RBC aplasia.

The treatment of choice for aplastic anemia is equine antithymocyte globulin (ATG) diluted in 500 mL of normal saline 10−20 mg/kg/day intravenous infusion over 4−6 hours for the next 10 days. Shorter regimens are also used. About 60% of patients respond to ATG.

Allergic reactions and serum sickness can occur; some experts prescribe intradermal skin testing (to identify allergy reaction to equine serum) and concomitant corticosteroids (Prednisone 40 mg/m^2/day as a single dose beginning from the 7th for 10 days or until symptoms subside). Cyclosporine (5−10 mg/kg/po/day) is as effective as ATG and yields responses for about 50% of ATG failures, suggesting that its mechanism of action is different. Combination of ATG and cyclosporine is also effective. If aplastic anemia is very severe or failed to respond to ATG and cyclosporine, bone marrow transplantation, or cytokine therapy (erythropoietin, interleukin-3 or granulocyte-macrophage colony-stimulating factor) are most effective.

Hematopoietic cell transplantation can help younger patients (particularly patients <30) but it requires an identical twin or

human leukocyte antigen identical sibling. Preimplantation genetic diagnosis was developed to evaluate human leukocyte antigen compatibility of unaffected siblings. Since transfusions increase the risks for the subsequent transplantation, blood products are used only if it is essential.

Pure RBC aplasia has been successfully managed by immunosuppressants (such as prednisone, cyclosporine, or cyclophosphamide), especially when an autoimmune disorder is suspected. Condition of the patients with thymoma-associated pure RBC aplasia is improved after thymectomy. Furthermore, computer tomography is used to detect such lesion, and the surgery operation is considered.

Section II. BLEEDING DISORDERS (HEMORRHAGIC DIATHESIS)

Hemostasis is a dynamic process mediated by interactions between the platelates and coagulaion factors in the plasma and the vessel wall. Von Willebrand factor (vWF) is the glycoprotein that plays an important role in stopping the escape of blood from vessels, following vascular injury, works by mediating platelet adhesion. Platelet activation is also mediated through shear forces imposed by blood flow itself, particularly in areas where the vessel wall is damaged, and is also affected by the inflammatory state of the endothelium.

The activated platelet surface provides the major physiologic site for coagulation factor activation, which is the result of further platelet activation and fibrin formation. Hemorrhagic diatheses are genetic and acquired diseases or syndromes with increased bleeding, abilities to repeated bleeding or hemorrage.

Unusual or excessive bleeding include unexplained nosebleeds (epistaxis), excessive or prolonged menstrual blood loss (menorrhagia), prolonged bleeding after minor cuts or

trauma, easy bruising in tissues (ecchymoses) or skin (petechial or purpuric lesions), and unexplained gingival bleeding after tooth brushing. Systemic bleeding may be caused by defects in blood vessels (connective tissue diseases, vitamin C deficiency, hereditary hemorrhagic telangiectasia) or by quantitative or qualitative platelet disorders (thrombocytopenia and platelet dysfunction), or by coagulation disorders in most cases.

Classification of hemorrhagic diathesis:

1. Thrombocytopenia and platelet dysfunctions:
   - idiopatic thrombocytopenic purpura (ITP);
   - thrombotic thrombocytopenic purpura (TTP);
   - hemolytic uremic syndrome (HUS);
   - thrombocytopenia due to splenic sequestration;
   - other causes of thrombocytopenia;
   - hereditary disorders of platelet function
   - coagulation disorders:
   - circulating anticoagulants;
   - disseminated intravascular coagulation (DIC);
   - hemophilia;
   - uncomon hereditary coagulation disorders;
   - bleeding due to abnormal blood vessels;
   - autoerythrocyte sensitization;
   - dysproteinemias causing vascular purpura;
   - hereditary hemorrhagic telangiectasia;
   - purpura simplex;
   - senile purpura.

Thrombocytopenia and Platelet Dysfunction. Etiology and Pathophysiology of Thrombocytopenia

Platelets are cellular fragments that function in the clotting system. Thrombopoetin, primarily produced in the liver as a

response of decreased numbers of marrow megakaryocytes and circulating platelets, stimulates the bone marrow to synthesize platelets from megakaryocytes. Platelets circulate from 7 to 10 days. About 1⁄3 is always transiently sequestered in the spleen. The normal platelet count in adults ranges from 150,000 to 450,000/μL (Tab. 7).

Table 7 − **Classification of thrombocytopenia**

Cause	Condition
Failed platelet production	
Decreased or absent megakaryocytes in the marrow	Leukemia, aplastic anemia, paroxysmal nocturnal hemoglobinuria (some patients), myelosuppressive drugs
Decreased platelet production despite the presence of megakaryocytes in the marrow	Alcohol-induced thrombocytopenia, thrombocytopenia during megaloblastic anemias, human immunodeficiency virus-associated thrombocytopenia, some myelodysplastic syndromes
Platelet sequestration in the enlarged spleen	Cirrhosis with congestive splenomegaly, myelofibrosis with myeloid metaplasia, Gaucher's disease
Increased platelet destruction or consumption	
Immune destruction of platelets	Immune thrombocytopenic purpura, also known as ITP, human immunodeficiency virus-associated TTP, post-transfusion purpura, drug-induced thrombocytopenia, neonatal alloimmune thrombocytopenia, connective tissue disorders, lymphoproliferative disorders
Nonimmune destruction of platelets	DIC, TTP, HUS, thrombocytopenia with acute respiratory distress syndrome
Dilution of platelets	Massive blood replacement or exchange transfusion (decrease in viability of stored blood)

The risk of bleeding is inversely proportional to the platelet count. When the platelet count is less than 50,000/μL, minor bleeding occurs easily and the risk of major bleeding increases. When the platelet count is between 20,000 and 50,000/μL there is a predispose of bleeding with trauma, even minor trauma. When the count is less than 20,000/μL, excess bleeding can occur. Severe spontaneous bleeding can also happen when platelet number is less than 5000/μL. However, patients with platelet counts less than 10,000/μL may be asymptomatic for years.

Symptoms and Signs

Often, low platelet count does not lead to clinical problems; rather, they are picked up on a routine complete blood count. Occasionally, there may be bruising, nosebleeds and/or bleeding gums. Platelet disorders result in a typical bleeding pattern with plural petechiae on the skin, typically most evident on the lower extremities; scattered small ecchymosis at sites of minor trauma; mucosal bleeding (a nosebleed, also known as epistaxis, bleeding in the GI and urogenital tracts, and vaginal bleeding); and excessive bleeding after surgery. Heavy GI bleeding and bleeding into the central nervous system can be life threatening. However, massive bleeding into tissues (e.g., deep visceral hematomas or hemarthroses) does not commonly occur and suggests a coagulation disorder (hemophilia) (Tab. 8).

Treatment

For patients with thrombocytopenia or platelet dysfunction, drugs that further impair platelet function should be avoided, particularly aspirin and other NSAIDs.

Patients may require platelet transfusion, but only in limited situations. Prophylactic transfusions are used sparingly because they may lose their effectiveness when it is repeated due to the

development of platelet alloantibodies.

In case of platelet dysfunction or thrombocytopenia caused by decreased platelet production, transfusions are reserved for active bleeding or severe thrombocytopenia (e.g., platelet count <10,000/μL). In thrombocytopenia caused by platelet destruction, transfusions are reserved for life-threatening or central nervous system bleeding.

Table 8 – **Peripheral blood smear in diagnosis of thrombocytopenic purpura**

Findings	Conditions
Normal morphology of RBCs and WBCs	ITP Gestational thrombocytopenia human immunodeficiency virus-related thrombocytopenia Drug-induced thrombocytopenia Post-transfusion purpura
RBC fragmentation	TTP-HUS Preeclampsia with DIC Metastatic carcinoma
WBC abnormalities	Immature cells or greater number of mature lymphocytes in leukemia Markedly reduced granulocytic, megakaryocytic, and erythrocytic cell lines in the bone marrow in aplastic anemia Hypersegmented polymorphonuclear leukocytes in megaloblastic anemias
Frequent giant platelets (approaching the size of RBCs)	Bernard-Soulier syndrome and other congenital thrombocytopenias
RBC abnormalities, nucleated RBCs, and immature granulocytes	Myelodysplasia

2.1. IDIOPATHIC THROMBOCYTOPENIC PURPURA

ITP is a bleeding disorder caused by thrombocytopenia which is not associated with a systemic disease. Typically, it is a chronic condition in adults but it is usually acute and self-limited in children. Spleen size is normal. Diagnosis requires other disorders to be excluded by selective tests.

ITP usually results from the development of antibodies directed against the structural platelet antigens (autoantibodies). In childhood ITP, the autoantibody can be triggered by binding viral antigen to megakaryocytes.

In children, ITP often persists for 2−3 weeks after a viral illness, with sudden onset of purpura and, sometimes, oral and nasal bleeding. It is important to ascertain that the child does not have any other systemic illness, particularly DIC. In adults, ITP most commonly affects females and has an insidious onset. Usually, in the history of the disease, there is a viral infection that precedes this disease. When the disease manifests, some cases may be associated with symptoms or signs of a connective tissue disease, whilst in other patients, these disorders may become apparent later in a few years. The condition is likely to become chronic, with remissions and relapses. The peripheral blood film is normal, apart from a greatly reduced platelet number, whilst the bone marrow reveals an obvious increase in megakaryocytes.

Symptoms, Signs, and Diagnosis:

- Petechiae and mucosal bleeding. The size of spleen is normal, unless it is enlarged by a coexistent childhood viral infection.
- ITP is suspected in patients with unexplained thrombocytopenia. Peripheral blood is normal except for a reduced number of platelets.

- Bone marrow should be examined if blood count or blood smear reveals abnormalities in addition to thrombocytopenia. Bone marrow examination reveals normal or possibly increased numbers of megakaryocytes in an otherwise normal marrow.

Because of nonspecific diagnostic findings, diagnosis requires exclusion of other thrombocytopenic disorders suggested by clinical or laboratory tests.

Human immunodeficiency virus testing is performed for patients at risk factors for human immunodeficiency virus infection, because human immunodeficiency virus-associated thrombocytopenia may be indistinguishable from ITP.

Treatment

Mild ITP does not require treatment.

When platelet count falls below 10,000/μL, or below 50,000/μL and hemorrhage occurs (e.g., in the digestive tract or in a severe nosebleed), treatment is usually begins with steroids. Corticosteroids (such as prednisone 1 mg/kg once/day) are rescue medicationes. In patients with a good response to the drug, the platelet count increases to normal within 2−6 weeks).

Intravenous immunoglobulin (Ig) is used in life-threatening cases. Later, so-called steroid-sparing agents may be used. If all previous actions did not produce a positive result, splenectomy is performed, because platelets, targeted for destruction are often destroyed in the spleen (about 2⁄3 of these patients can achieve a remission). In a child or an adult with ITP and life-threatening bleeding, a rapid phagocytic blockade is attempted by giving intravenous Ig 1 g/kg once/day for 1 to 2 days. As a result, the platelet count increases in 2−4 days, but only for 2−4 weeks.

Extreme cases are very rare, especially in children, and require an immunosuppressive treatment (chemotherapy

agents: cyclophosphamide, azathioprine, rituximab) to prevent the destruction of platelets by immune system.

A platelet transfusion is usually not recommende, and usually it does not contribute to an increase in the patient's platelet count. This happens because of underlying autoimmune mechanisms that destroy the patient's platelets and stimulate the process of destruction of donor platelets. A notable exception is heavy bleeding, when platelet transfusion can form a platelet plug to stop bleeding very quickly.

Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome

This is a rare cause of thrombocytopenia presented by a variety of specialties that requires urgent management. Platelets become activated by thrombin and form platelet aggregate in the microvasculature, affecting the renal and cerebral circulation in particular. Excessive platelet aggregation is believed to occur because of unsufficient functioning of protease enzyme that results in the presence of ultralarge vWF. It can be associated with drugs, autoimmune disease, and infections (e.g., E. Coli).

Symptoms and Signs

Unexplained thrombocytopenia and microangiopathic hemolytic anemia are sufficient evidences for a presumptive diagnosis.

TTP-HUS are suspected in patients with suggestive symptoms, thrombocytopenia, and anemia. If the disease is suspected, urinalysis, peripheral blood smear, reticulocyte count, serum lactate dehydrogenase, renal functions, serum bilirubin (direct and indirect), and Coombs' test are obtained. The proposed diagnosis − thrombocytopenia and anemia, with fragmented RBCs on the blood smear (helmet cells, triangular shaped, fragmented or greatly distorted RBCs – all these

changes describe microangiopathic hemolysis); evidence of hemolysis (decreased Hb level, polychromasia, increased reticulocyte count, increased lactate dehydrogenase); and negative direct antiglobulin (Coombs) test.

Prognosis and Treatment

Epidemic HUS in children caused by enterohemorrhagic infection usually spontaneously remites and is treated with supportive care. In other cases, untreated TTP-HUS is almost always fatal.

However, about 85% of patients with plasma exchange recover completely. Plasma exchange continues daily for several days or weeks until signs of disease activity disappear.

The use of corticosteroids and antiplatelet agents (aspirin) in TTP is still controversial, but may be reasonable.

Thrombocytopenia Due to Splenic Sequestration

Increased splenic platelet sequestration can occur in various disorders that cause splenomegaly. Sequestration is expected in patients with congestive splenomegaly caused by advanced cirrhosis. The platelet count is usually over 30,000/μL unless the disorder causcing the splenomegaly also impairs platelet production (e.g., in myelofibrosis with myeloid metaplasia).

Thrombocytopenia: Other Causes:

- acute respiratory distress syndrome;
- blood transfusions;
- connective tissue and lymphoproliferative disorders
- drugs-induced immunologic destruction: commonly used drugs that occasionally induce thrombocytopenia (aspirin, indometacin, gold salts methyldopa, oral antidiabetic drugs, penicillins, cephalosporins, carbamazepine, rifampicin, sulfa preparations, dextran, heparin, and b-blockers);
- gram-negative sepsis;

- human immunodeficiency virus.

Qualitative Disorders of Platelet Function. Inherited Disorders of Platelet Function

Inherited platelet function disorders are thought to be relatively rare, although the prevalence of mild disorders in platelet function is unclear, partially because of suboptimal testing for such disorders.

Thrombasthenia (Glanzmann's disease) is a rare autosomal recessive disorder caused by a defect in the platelet glycoprotein IIb-IIIa complex; platelets cannot aggregate. Patients may experience severe mucosal bleeding (e.g., nosebleeds, finished only after nasal packing and transfusions of platelet concentrates).

Bernard-Soulier syndrome is another rare autosomal recessive disorder. It impairs platelet adhesion due to the defect in the glycoprotein Ib-IX complex. The bleeding can be rather severe. Platelets are unusually large. They do not aggregate upon addition of ristocetin, but normally aggregate to collagen, and epinephrine.

Both are inherited in an autosomal recessive fashion and present bleeding symptoms in childhood. Platelet storage pool disorder is an autosomal dominant qualitative platelet disorder. This is a result of abnormalities in platelet granule formation. Hermansky-Pudlak syndrome also consists of inherited disorders of granule formation.

Bleeding symptoms are variable in storage pool disorder, but often mild. The most common inherited disorders of platelet function are disorders that prevent normal secretion of granule content. Several abnormalities have been removed at the molecular level, but they are probably associated with multiple abnormalities. They are usually described as secretion defects. Bleeding symptoms are usually mild.

Treatment

Bleeding symptoms and prevention of bleeding in patients with severe dysfunction often require platelet transfusion. In order to limit the risk of alloimmunization one should limit exposure and use prestorage leukodepleted platelets for transfusion. Platelet disorders, associated with mild bleeding symptoms, often respond to desmopressin or 1-deamino-8-D-arginine vasopressin (DDAVP). DDAVP increases plasma levels of factor VIII and vWF; it is not known whether it also has a direct effect on the function of platelets. In particular, with mucosal bleeding symptoms, antifibrinolytic therapy (epsilon-aminocaproic acid or tranexamic acid) is used alone or in combination with DDAVP or platelet therapy.

Hereditary Intrinsic Platelet Disorders.

Von Willebrand's Disease

Von Willebrand's disease (vWD) is a hereditary deficiency of von Willebrand factor (vWF), which causes platelet dysfunction.

vWF is synthesized and secreted by vascular endothelium to form part of the perivascular matrix. vWF promotes the platelet adhesion phase of hemostasis by binding with a receptor on the platelet surface membrane (glycoprotein Ib-IX), which connects the platelets to the vessel wall. vWF is also required to maintain normal plasma factor VIII levels.

Disorders of amplification of platelet activation are the most common hereditary intrinsic platelet disorders and produce mild bleeding. They are able to be the result of decrease of adenosine diphosphate in the platelet granules (storage pool deficiency), connected with the inability of generation of thromboxane A2 from arachidonic acid, or with inability of platelets to aggregate thromboxane A2.

Symptoms and Signs

Bleeding manifestations are mild to moderate and include easy bruising; bleeding from small skin cuts that may stop and start over hours; sometimes, increased menstrual bleeding; and abnormal bleeding after surgical procedures (e.g., tooth extraction, tonsillectomy).

Diagnosis of Von Willebrand's Disease

vWD is suspected in patients with bleeding disorders, particularly with a family history of the disorder.

Definitive diagnosis requires measuring total plasma vWF antigen; vWF function, which is determined by the ability of plasma to support agglutination of normal platelets by ristocetin (ristocetin cofactor activity); and plasma factor VIII level.

Treatment of Von Willebrand's Disease

Patients are treated only if they are actively bleeding or are undergoing an invasive procedure (surgery, dental extraction).

The treatment involves replacement of vWF by infusion of pasteurized concentrates of intermediate-purity factor VIII, containing the components of vWF. These concentrates are virally inactivated and, therefore, they do not transmit human immunodeficiency virus infection or hepatitis. These concentrates are preferable to cryoprecipitate, commonly used before, because they cannot cause transfusion-transmitted infections.

High-purity concentrates of factor VIII are prepared by immunoaffinity chromatography and do not contain vWF.

2.2. COAGULATION DISORDERS CAUSED BY CIRCULATING ANTICOAGULANTS

Circulating anticoagulants (CA) may be defined as

autoantibodies that neutralize specific clotting factors in vivo (autoantibody against factor VIII or factor V) or inhibit protein-bound phospholipid in vitro.

Antibodies bind to prothrombin-phospholipid complexes, inducing hypoprothrombinemia; these patients may bleed excessively.

Factor VIII autoantibodies also arise occasionally in nonhemophilic patients, e.g., in a postpartum woman as a manifestation of underlying systemic autoimmune disease or in elderly patients without overt evidence of other underlying disease. The life-threatening hemorrhage can be caused by factor VIII anticoagulant.

Therapy with cyclophosphamide and corticosteroids may suppress autoantibody production in patients without hemophilia.

Disseminated Intravascular Coagulation (Coagulopathy or Defibrination Syndrome)

DIC involves abnormal, excessive generation of thrombin and fibrin in the circulating blood. In the process, increased platelet aggregation and coagulation factor consumption occur. DIC that develops slowly (withing a few weeks or months) primarily causes venous thrombotic and embolic manifestations; DIC, that evolves rapidly (withing a few hours or days), primarily causes bleeding.

Etiology and Pathophysiology of DIC

– complications of obstetrics, e.g., placental abruption, hypertonic saline-induced abortion, retained dead fetus or dead products of conception, or amniotic fluid embolism;

– infection, particularly with Gram-negative bacteria;

– malignancy, particularly mucin-secreting adenocarcinomas of the pancreas and prostate and acute promyelocytic leukemia;

– any cause of shock;

– severe tissue damage from head trauma, burns, frostbite burns, or gunshot wounds; complications of prostate surgery;

– venomous snake bites with enzymes entering of enzymes the circulatory system, activating one or more clotting factors and generating thrombin, or directly converting fibrinogen to fibrin;

– profound intravascular hemolysis;

– aortic aneurysms or cavernous hemangiomas (Kasabach-Merritt syndrome) associated with vessel wall damage and areas of blood stasis.

Symptoms and Signs of DIC

During a slowly evolving DIC, symptoms of venous thrombosis and pulmonary embolism may be present.

In a severe, rapidly evolving DIC, skin puncture sites (e.g., venous or arterial punctures) bleed persistently; ecchymosis is formed at the site of parenteral injection; and serious GI bleeding may occur. Delayed dissolution of fibrin polymers by fibrinolysis may result in the mechanical disruption of RBCs and mild intravascular hemolysis (see section Thrombocytopenia and Platelet Dysfunction: TTP and HUS). Occasionally, microvascular thrombosis and hemorrhagic necrosis produce dysfunction and failure in multiple organs.

Diagnosis of DIC:

- decreased plasma fibrinogen;
- increased plasma D-dimer (an indication of cross-linked fibrin deposition and degradation);
- thrombocytopenia, activated partial thromboplastin time (APTT) and less often prothrombin time (PT) may be minimally prolonged (results are typically reported as international normalized ratio);
- the level of factor VIII decreased in DIC, because

thrombin-induced generation of activated protein C cause proteolysis of factor VIII.

Treatment of DIC:

- immediate correction of underlying cause is the priority (e.g., broad-spectrum antibiotic treatment of suspected gram-negative sepsis, evacuation of the uterus in placental abruption);
- if treatment is effective, DIC would quickly subside; if bleeding is severe, adjunctive therapy with clotting factor replacement is indicated, consisting of platelet concentrates to correct thrombocytopenia;
- cryoprecipitate for replacement of fibrinogen and factor VIII;
- fresh frozen plasma for increasing the levels of other clotting factors and natural anticoagulants (antithrombin, proteins C and S).

HEMOPHILIA

Hemophilias are common hereditary bleeding disorders caused by deficiencies of one or several clotting factors such as VIII or IX.

Hemophilia A (factor VIII deficiency), which affects about 80% of hemophilic patients, and hemophilia B (factor IX deficiency) have identical clinical manifestations, screening test abnormalities, and X-linked genetic transmission.

Hemophilia affects males almost exclusively because of location of the genes on the X chromosome. Daughters of hemophilic males are obligate carriers, but sons are not carriers. Each son of the carrier has a 50% chance of having hemophilia, and each daughter has a 50% chance of being a carrier.

Diagnosis:

- patients with hemophilia has bleeding into tissues (e.g., hemarthroses, muscle hematomas, and retroperitoneal hemorrhage); the bleeding may delayed after trauma. Synovitis and arthropathy may be caused by hemarthroses;
- family history;
- APTT, blood clotting time, plasma recalcification time are prolonged, but the PT, bleeding time and platelet count are normal;
- low levels of factor VIII and IX.

Prevention and Treatment

It is important to avoid aspirin and NSAIDs due to the risk of GI bleeding. Selective cyclooxygenase-2 inhibitors have comparable analgetic effect to traditional NSAIDs but with less upper a bleeding, and can be used with caution for hemophilia.

Drugs should be given orally or IV to avoid surgical operations.

Factor VIII is used to prevent bleeding in hemophilia A.

Factor IX is used to treat hemophilia B.

A temporary increase in the level of factor VIII may be caused by desmopressin (other trade names Ddavp, Stimate).

An antifibrinolytic agent such as ε-aminocaproic acid, marketed Amicar (2.5 to 4 g po qid for 1 wk), or tranexamic acid, marketed as Cyklokapron (1.0 to 1.5 g po tid or qid for 1 wk), should be given to prevent late bleeding after dental extraction or other oropharyngeal mucosal trauma (e.g., tongue laceration).

2.3. BLEEDING DUE TO ABNORMAL BLOOD VESSELS

Bleeding can be caused by platelet dysfunction, coagulation disorders, or damaged blood vessels. Vascular bleeding

disorders are caused by defects of blood vessels, typically producing petechiae, purpura, and bruising, but seldom leading to serious blood loss. Bleeding may be caused by deficiencies of vascular and perivascular collagen in Ehlers-Danlos syndrome and in other rare hereditary tissue disorders (such as pseudoxanthoma elasticum, osteogenesis imperfecta, and Marfan syndrome). Hemorrhage may be a prominent clinical feature of scurvy (Vitamin C deficiency) or Henoch-Schönlein purpura (HSP), a hypersensitivity vasculitis, most common in childhood. For vascular bleeding disorders, screening tests of hemostasis are usually normal. Diagnosis is clinical.

Cryoglobulinemia

Cryoglobulins are serum Igs that precipitate when plasma is cooled while flowing through the skin and subcutaneous tissues of the extremities.

Monoclonal immunoglobulin, formed in Waldenström's macroglobulinemia or in multiple myeloma, occasionally behaves as cryoglobulins, since it may be mixed into IgM-IgG immune complexes formed in some chronic infections, most often in hepatitis C.

Cryoglobulinemia can lead to small-vessel vasculitis, which can produce purpura. Cryoglobulins can be detected by laboratory testing.

Hypergammaglobulinemic purpura is a vasculitic purpura that primarily affects women. Recurrent crops of small palpable purpuric lesions develop on the lower legs. These lesions leave small residual brown spots. Many patients have manifestations of an underlying immunologic disorder (Sjögren's syndrome). Diagnostic defection is a polyclonal increase in IgG (broad-based or diffuse hypergammaglobulinemia on serum protein electrophoresis).

Purpura and other forms of abnormal bleeding (profuse epistaxis) in patients with Waldenström's macroglobulinemia

may be caused by hyperviscosity syndrome which is a result of markedly increased serum IgM concentration.

VESSEL WALL ABNORMALITIES

Vessel wall abnormalities may be congenital such as hereditary haemophilia telangiectasis, or acquired as for vasculitis.

Hereditary haemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)

Patients experience recurrent bleeding, in particular epistaxis, or iron deficiency associated with latent GI bleeding. Treatment may be difficult because of the multiple bleeding points, but regular iron therapy often stimulates the bone marrow to compensate for the blood loss. Local cautery or laser therapy may prevent single lesions from bleeding. A variety of medical therapies have been tried, but none has been found to be universally effective.

Ehlers-Danlos Disease

The Ehlers-Danlos disease is an inherited disorder of collagen synthesis of the connective tissue which is expressed by joint hyperextensibility, skin extensibility and tissue fragility such that capillaries, poorly supported by subcutaneous collagen and ecchymoses, are commonly visible.

Hereditary Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia is a hereditary disease of vascular malformation that is transmitted as an autosomal dominant trait that affects both men and women. It is manifested by mucocutaneous telangiectasis and arteriovenous malformations.

Lessions can affect the nasopharynx, central nervous system, lung, liver, spleen, GI tract, urinary tract, conjuctiva,

arms and fingers.

Some patients have pulmonary arteriovenous fistulas. These fistulas may produce massive right-to-left shunts which may cause dyspnea, fatigue, cyanosis, or polycythemia.

However, the first sign of their presence may be a brain abscess, transient ischemic attack, or stroke which is a result of infected or noninfected embolia. Cerebral or spinal arteriovenous malformations occur in some families and may cause the subarachnoid hemorrhage, seizures, or paraplegia.

Symptoms, Signs, and Diagnosis

The most characteristic lesions are small red-to-violet telangiectatic lesions on the face, lips, oral and nasal mucosa, and tips of the fingers and toes. Similar lesions may be present throughout the mucosa of the GI tract, resulting in recurrent GI bleeding.

Treatment

Treatment can be difficult because of the multiple bleeding points but regular iron therapy often allows the bone marrow to compensate for blood loss. Local cautery or laser therapy can prevent single lesions or bleeding. A wide variety of medical therapies has been tried but none has been found to be universally effective.

Treatment for most patients is supportive, but available telangiectasias can be cured by laser ablation.

Arteriovenous fistulas can be treated by surgical resection or embolotherapy.

2.4. HENOCH-SCHÖNLEIN PURPURA

HSP, or anaphylactoid purpura, is a distinct, self-limited type of vasculitis that affects children and young adults. The patients have an acute inflammatory response to IgA and complement components in capillaries, mesangial tissues and

arterioles, leading to increased vascular permeability and localized hemorrhage. The syndrome is often preceded by an upper respiratory infection, commonly with streptococcal pharyngitis, or triggered by drug or food allergies. Purpuric rashes appear on the extensor surfaces of arms and legs, usually accompanied by polyarthralgias or arthritis, abdominal pain, and reccurent hematuria from focal glomerulonephritis. All coagulation tests are normal, but may result in impaired renal function.

HSP is an immune complex vasculitis that affects primarily small vessels. It most commonly affects children.

Common manifestations include palpable purpura, arthralgias, GI symptoms and signs, and glomerulonephritis.

The diagnosis is clinical for children but usually warrants biopsy in adults. Disease is usually self-limited.

Corticosteroids can relieve arthralgias and GI symptoms but do not alter the course of the disease. Progressive glomerulonephritis may require high-dose corticosteroids and cyclophosphamide.

Symptoms and Signs of HSP

The primary sign of the disease is sudden palpable purpuric skin rash, typically on the feet, legs, and arms and as a strip across the buttocks. The purpura may start as small areas of urticaria that become indurated and palpable. Crops of new lesions may appear after several days or a few weeks. Many patients also have fever and polyarthralgia with periarticular tenderness and swelling that affect ankles, knees, hips, wrists, and elbows.

GI symptoms are common and include colicky abdominal pain, abdominal tenderness, and melena. Symptoms usually remit after about 4 weeks. For most patients, the disorder subsides without serious sequelae; however, some patients develop chronic renal failure.

Diagnosis of HSP:

- biopsy of skin lesions;
- the diagnosis is suspected in patients, particularly children, with typical skin findings. It should be confirmed by biopsy of skin lesions when leukocytoclastic vasculitis with IgA deposits in blood vessel walls is identified;
- urine analysis should be performed. Hematuria, proteinuria, and RBC casts indicate renal involvement;
- if renal function deteriorates, renal biopsy may help to define the prognosis. Diffuse glomerular involvement or crescent formation in most glomeruli predictes progressive renal failure.

Treatment of HSP

Treatment is symptomatic. Corticosteroids (prednisone 2 mg/kg up to a total of 50 mg po once/day) may help to control abdominal pain and are occasionally needed to treat severe joint pain or renal disease. Pulse IV methylprednisolone followed by oral cyclophosphamide which can be given for attemption to control inflammation when kidneys are severely affected. However, the effects of corticosteroids associated with renal manifestations are not clear.

Autoerythrocyte Sensitization (Gardner-Diamond Syndrome)

Autoerythrocyte sensitization is a rare disorder which is most common in women. It is characterized by local pain and burning that precede painful ecchymotic lesions, mostly on the extremities.

In some women with autoerythrocyte sensitization, intradermal injection of 0.1 mL of autologous RBCs or RBC stroma may cause pain, swelling, and induration at the injection site.

The diagnosis is based on the study of the site of intradermal

injection of autologous RBCs and a separate site of control injection (without RBCs) within 24−48 hours after the injection.

Dysproteinemias Causing the Vascular Purpura

Amyloidosis causes intracellular amyloid deposition within vessels in organs and tissues, throughout the body, which can increase vascular fragility and produces purpura. In some patients, coagulation factor X is adsorbed by amyloid fibrils and becomes deficient, but this is not usually the cause of bleeding. Periorbital purpura or a purpuric rash that developes in a nonthrombocytopenic patient after gentle stroking of the skin suggests amyloidosis.

Purpura Simplex (Easy Bruising Syndrome)

Purpura simplex is a condition characterized by easy bruising due to vascular fragility.

Purpura simplex is very common. The cause and mechanism are unknown. It may represent a heterogeneous group of disorders.

This disorder usually affects women. Bruises develop without known trauma on the thighs, buttocks, and upper arms. There is no abnormal bleeding in the history, but there is the possibility of easy bruising in family members. Serious bleeding does not occur. The platelet count and tests of platelet function, blood coagulation, and fibrinolysis are normal.

There are no drugs for preventing bruising. The patients are advised to avoid aspirin that can increase their chance of bruising.

Senile Purpura

Senile purpura produces ecchymoses, and it is the result of increased vessel fragility due to the damage of dermal connective tissue, caused by to the dermis caused by chronic

sun exposure and aging.

Senile purpura affects older patients who develop persistent dark purple ecchymoses, which are characteristically confined to the extensor surfaces of the hands and forearms. New lesions appear without known trauma, and then resolve over several days, leaving a brownish discoloration caused by deposits of hemosiderin. Discoloration lasts from weeks to months. The skin and subcutaneous tissue of the involved area often appear to be thinned and atrophic. There is no treatment for lesion resolution. The disorder has no serious health consequences, though it is cosmetically displeasing.

Section III. HEMOBLASTOSIS (Leukemias)

Definition

Leukemias are cancers of the WBCs involving bone marrow, circulating WBCs, and such organs as the spleen and lymph nodes.

Etiology:

- history of exposure to ionizing radiation (e.g., after atomic bombings of Nagasaki and Hiroshima) or chemicals (benzene);
- prior therapy using certain antineoplastic drugs, particularly procarbazine, nitrosoureas (cyclophosphamide and melphalan), and epipodophyllotoxins (etoposide and teniposide);
- viruses or infections agents associated with human cancer etiology (such as human T-lymphotropic virus I and II, and Epstein-Barr virus);
- chromosomal translocations;
- preexisting conditions that include immunodeficiency disorders, chronic myeloproliferative disorders, and chromosomal disorders (Fanconi's anemia, Bloom syndrome,

ataxia-telangiectasia, Down syndrome, and infantile X-linked agammaglobulinemia).

3.1. LEUKEMIAS

Pathophysiology

Malignant transformation usually occurs at the pluripotent stem cell level, although sometimes it involves a committed stem cell with limited capacity for differentiation. Abnormal proliferation, clonal expansion, and diminished apoptosis (programmed cell death) lead to replacement of normal blood elements by malignant cells.

Clinical manifestations of leukemia are caused by suppression of normal blood cell formation and organ infiltration of leukemic cells. Inhibitory factors produced by leukemic cells and replacement of marrow space are able to suppress normal hematopoiesis, with ensuing anemia, thrombocytopenia, and granulocytopenia. The enlargement of the liver, spleen, and lymph nodes, with occasional kidney and gonadal involvement, are caused by organ infiltration. Meningeal infiltration connected with clinical features is associated with increasing intracranial pressure (cranial nerve palsies).

Classification

Acute leukemias consist of predominantly immature, poorly differentiated cells (usually blast forms); in chronic leukemias, blast cells are more mature. Acute leukemias are divided into lymphoblastic (ALL) and myeloid (AML) types, and may be further subdivided by the French-American-British (FAB) classification (Table 9).

Chronic leukemias are described as lymphocytic (CLL) or myeloid (CML).

Myelodysplastic syndromes are often referred to as

progressive bone marrow failure but with an insufficient proportion of blast cells (<30%) for making a definite diagnosis of AML; From 40 to 60% of MDS cases evolve into AML.

A leukemoid reaction is defined as granulocytic leukocytosis (WBC >30,000/μL) produced by normal bone marrow in response to of systemic infection or cancer. Although there is a non-neoplastic disorder, a leukemoid reaction with a very high WBC count may require testing to distinguish it from CML.

Table 9 – **The French-American-British classification of acute leukemias**

Leukemia and FAB Classification	**Description**
Acute Lymphoblastic Leukemia	
L1	Lymphoblasts with uniform, round nuclei and scant cytoplasm
L2	More variable lymphoblasts; sometimes nuclei are irregular with more abundant cytoplasm than in L1 subtype
L3	Lymphoblasts with finer nuclear chromatin and blue to deep blue cytoplasm that contains vacuoles

FAB Classification of Acute Lymphoblastic Leukemia: L1 Subtype

The L1 subtype is characterized by small (10−15μ) cells, with round, finely reticulated to coarse chromatin, some nuclear indentation, sparse, slightly basophilic cytoplasm, and

absence of nucleoli.

L1 lymphoblasts are distinguished from normal mature lymphocytes by the homogeneity of their chromatin structure and their monotonous appearance.

FAB Classification of Acute Lymphoblastic Leukemia: L2 Subtype

The L2 subtype is characterized by medium-sized (14−18μ) cells with more heterogeneity in cell size. These lymphoblasts have fine chromatin, nuclear indentation and tight folding in some cells, basophilic cytoplasm, and nucleoli.

L2 lymphoblasts are distinguished from myeloblasts by the variation of size, more basophilic cytoplasm, and lack of granules.

FAB Classification of Acute Lymphoblastic Leukemia: L3 Subtype

The L3 subtype is characterized by homogeneous, medium-sized to large cells with round, demarcated, and finely punctuated chromatin, no folding, deeply basophilic and vacuolated cytoplasm, and nucleoli. Some apoptosis and fragmentation are usually seen.

Vacuoles in the cytoplasm are not pathognomonic in L3, and other features (e.g., specific cytogenetic and immunologic characteristics) must be considered to make a definitive diagnosis (Table 10).

Acute Promyelocytic Leukemia

Acute promyelocytic leukemia is usually the most easily diagnosed acute myeloid leukemia because cytoplasm of the malignant cells is repleted with large eosinophilic granules and Auer rods. The nuclei are often multilobed with undistinguishable nucleoli and are heavily weighted with variably colored granules

Table 10 − **Acute myeloid leukemia**

Acute Myeloid Leukemia	
M1	Acute myeloblastic leukemia without maturation of blasts
M2	Acute myeloblastic leukemia; with maturation of blasts
M3	Acute promyelocytic leukemia; with a characteristic pattern of heavy granulation granulation
M4	Acute myelomonocytic leukemia with mixed myeloblastic and monocytoid morphology
M5	Acute monoblastic leukemia; pure monoblastic morphology
M6	Acute erythroleukemia, with predominantly immature erythroblastic morphology, sometimes including megaloblastic features
M7	Acute megakaryoblastic leukemia; majority of cells are megakaryoblastic

Acute Myeloid Leukemia Without Maturation (FAB AML-M1)

In acute myeloid leukemia without maturation (AML-M1), the malignant cells differ according to their shape, but they are homogeneous in staining quality.

There are nuclear chromatin with a characteristic ground-glass texture, pale punched-out nucleoli, and a modest amount of cytoplasm in the blasts.

Myeloperoxidase cytochemistry and the presence of background dysplastic myeloid cells usually distinguish these primitive cells from lymphoblasts (Tab. 11).

Blasts With Monocytic Differentiation

The acute myelomonocytic leukemia, acute monoblastic leukemia, and acute monocytic leukemia are representatives of myeloid leukemias with cytologic and cytochemical features of monocytic differentiation, according to the World Health Organization classification. They correspond to acute myeloid leukemia (AML) FAB-M4, M5a, and M5b.

These 3 subtypes of AML differ solely in what percentage of immature cells show cytochemical evidence of monocytic differentiation and whether those immature cells are more or less mature. Promonocytes − immature cells, but they retain some features of mature monocytes such as folded and convoluted nuclear contours with a moderate amount of vacuolated cytoplasm. Monoblast cells have an ameboid quality, with round to oval nuclei containing delicate chromatin, prominent nucleoli, and abundant cytoplasm.

Table 11 − **Diagnosis of the common types of leukemia**

Feature	**Acute lymphoblastic Leukemia**	**Acute Myeloid Leukemia**	**Chronic lympho-cytic Leukemia**	**Chronic Myeloid Leukemia**
Peak age of incidence	Childhood	Any age	Middle and old age	Young adulthood
WBC count	High in 50% Normal or low in 50%	High in 60% Normal or low in 40%	High in 98% Normal or low in 2%	High in 100%
WBC differen-tial count	Many lympho-blasts	Many myeloblasts	Small lympho-cytes	Entire myeloid series
Anemia	Severe in >90%	Severe in >90%	Mild in about 50%	Mild in 80%
Platelets	Low in >80%	Low in >90%	Low in 20−30%	High in 60% Low in 10%
Lymph-adenopathy	Common	Occasional	Common	Infrequent
Spleno-megaly	In 60%	In 50%	Usual and moderate	Usual and severe

Table 11 (cont.)

Feature	Acute lympho-blastic Leukemia	Acute Myeloid Leukemia	Chronic lymphocytic Leukemia	Chronic Myeloid Leukemia
Other fea-tures	Without prophylaxis; CNS involvement	CNS rare involvement is; Auer rods are sometimes seen in myeloblasts	Occasional autoimmune hemolytic anemia and hypo-gamma-globulinemia	Leukocyte alkaline phosphatase score is low; Philadelphia chromosome positive CML in >90%

3.1.1. ACUTE LEUKEMIA

Acute leukemia occurs when hematopoietic stem cell undergoes a malignant transformation into a primitive, undifferentiated cell with an abnormal longevity. Such lymphocytes (ALL) or myeloid cells (AML) proliferate abnormally, replacing normal marrow tissue and hematopoietic cells, and inducing anemia, thrombocytopenia, and granulocytopenia. They can infiltrate various organs and sites such as the liver, spleen, lymph nodes, central nervous system, kidneys, and gonads because they are bloodborne.

Symptoms and Signs

Symptoms may persist for several days or weeks before diagnosis.

Disrupted hematopoiesis is the cause of the most common present symptoms (e.g., anemia, infection, easy bruising and bleeding). Other present symptoms and signs (e.g., pallor, fatigue, fever, malaise, weight loss, tachycardia, and chest

pain) are usually nonspecific and attributable to anemia and a hypermetabolic state. Often, the cause of fever is not found, although granulocytopenia may cause a rapidly progressing and potentially life-threatening bacterial infection.

Bleeding is usually manifested by petechiae, easy bruising, epistaxis, bleeding gums, or menstrual irregularity. Hematuria and GI bleeding are uncommon.

Bone marrow and periosteal infiltration may cause bone and joint pain.

Initial central nervous system involvement or leukemic meningitis (manifested as headaches, vomiting, irritability, cranial nerve palsies, seizures, and papilledema) is uncommon.

Extramedullary infiltration by leukemic cells may cause lymphadenopathy, splenomegaly, hepatomegaly, and leukemia cutis (a raised, nonpruritic rash).

Diagnosis:

- CBC and peripheral smear;
- Bone marrow examination;
- Histochemical studies, cytogenetics, immunophenotyping, and molecular biology studies.

Specific B-cells, T-cells, and myeloid-antigen monoclonal antibodies, together with flow cytometry are important.

Other laboratory findings may detect hyperuricemia, hyperphosphatemia, hyperkaliemia or hypokaliemia, elevated serum hepatic transaminases or lactate dehydrogenase, hypoglycemia, and hypoxia. Lumbar puncture and head computer tomography are typically done for patients with central nervous system symptoms, B-cell ALL, high WBC count, or high lactate dehydrogenase. Chest x-ray is done to detect a mediastinal masses. Computer tomography, magnetic resonance imaging, or abdominal ultrasonography may help assess splenomegaly or leukemic infiltration of other organs.

Peripheral blood smear is a basic and highly informative

diagnostic test; pancytopenia and peripheral blasts are the indicators of acute leukemia. The level of blast cells in the peripheral smear is 90% unless the WBC count is markedly decreased.

Bone marrow examination (aspiration or needle biopsy) should be always done. The level of blast cells in the bone marrow is 20–95 and 95% in case of acute leukemia.

The percentage of blast cells in peripheral blood should be determined.

It is necessary to make the differential diagnosis of severe pancytopenia with the following disorders:

- aplastic anemia;
- viral infections such as infectious mononucleosis;
- vitamin B12 and folate deficiency.

Prognosis

Both ALL and AML treatment gives good results especially in younger patients. Prognosis is worse in infants and the elderly persons and in patients with hepatic or renal dysfunction, central nervous system involvement, myelodysplasia, or a high WBC count (>25,000/μL). Survival in untreated acute leukemia is generally 3 to 6 months. Prognosis varies according to karyotype.

Treatment:

- chemotherapy;
- supportive care.

Supportive care include the following activities:

- transfusions;
- antibiotics or antifungal drugs;
- hydration and urine alkalinization;
- psychologic support.

The goal of treatment is complete remission, restoration of

normal blood counts and normal hematopoiesis, with less than 5% blast cells, and elimination of the leukemic clone. Although basic principles of ALL and AML treatment are similar, the drug regimens differ.

Transfusions

Transfusions of platelets, RBCs, and granulocytes are administered to patients with bleeding, anemia, and neutropenia, respectively. Prophylactic platelet transfusion is done when platelets are less than 10,000/μL; a higher threshold (20,000/μL) is used for patients with the triad of fever, disseminated intravascular coagulation, and mucositis secondary to chemotherapy. Anemia (Hb<8g/dL) is treated with packed RBC transfusions. Granulocyte transfusions may help neutropenic patients with Gram-negative or other serious infections, but such benefit as prophylaxis is absent.

Antimicrobial drugs are often nesessary because of the seriousness of infections in neutropenic and immunosuppressed patients, and infections can progress very quickly without usual early clinical manifestation. According to the results of appropriate studies and cultures, it is necessary to prescribe broad-spectrum bactericidal antibiotics that are effective against Gram-positive and Gram-negative organisms to both febrile and afebrile patients with neutrophil counts <500/μL.

Hydration (twice the daily maintenance volume), urine alkalinization (pH 7 to 8), and electrolyte monitoring can prevent the hyperuricemia, hyperphosphatemia, and hyperkalemia (i.e., tumor lysis syndrome) caused by the rapid lysis of leukemic cells during initial therapy (particularly in ALL). Hyperuricemia can be minimized by giving allopurinol.

Chronic Leukemia

Chronic leukemia is usually manifested as abnormal leukocytosis with or without cytopenia in an otherwise

asymptomatic persons. Findings and management are different for chronic lymphocytic leukemia (CLL) and chronic myelocytic leukemia (CML).

3.1.2. PATHOPHYSIOLOGY OF CHRONIC LYMPHOCYTIC LEUKEMIA

There is a malignant transformation of CD5+ B cells in 98% of cases, with initial accumulated lymphocytes in the bone marrow, lymph nodes and other lymphoid tissues, eventually induced splenomegaly and hepatomegaly.

Anemia, neutropenia, thrombocytopenia, and decreased immunoglobulin production are caused by abnormal hematopoiesis as a result of the progress of CLL. A lot of patients have hypogammaglobulinemia and impaired antibody response, perhaps related with increased cellular activity of suppressor T cells. The patients have increased susceptibility to autoimmune disease characterized by immunohemolytic anemias (usually Coombs' test–positive) or thrombocytopenia and a modestly increased risk of the development of other cancers.

Difference Between Typical CLL and Other Chronic Leukemias

The clonal neoplastic expansion of type T cells is a sign of 2–3% of cases. This subtype (large granular lymphocytes with cytopenias) is characteristic for the following groups:

- T-cell prolymphocytic leukemia;
- leukemic phase of cutaneous T-cell lymphoma (Sezary syndrome);
- hairy cell leukemia;
- lymphoma of T-cell leukemia (leukemic changes that occur at the advanced stages of malignant lymphoma).

Symptoms and Signs

The onset is usually insidious; CLL is often diagnosed incidentally during routine blood tests or through evaluation of asymptomatic lymphadenopathy. Symptomatic patients usually have nonspecific complaints of fatigue, anorexia, weight loss, dyspnea on exertion, or a sense of abdominal fullness (secondary to an enlarged spleen). Initial findings include generalized lymphadenopathy, minimal-to-moderate hepatomegaly and splenomegaly. The progress of the disease can cause pallor as a result of anemia. Skin infiltration, either maculopapular or diffuse, can be a feature of T-cell CLL.

Hypogammaglobulinemia and granulocytopenia in late CLL can predispose to bacterial, viral, and fungal infections, especially pneumonia. Herpes zoster is common, and it usually affects the skin of the asociated dermatome.

Diagnosis of CLL:

- peripheral smear;
- bone marrow examination;
- immunophenotyping;

- CLL is confirmed by examining the peripheral smear and bone marrow; the hallmark is sustained level of absolute peripheral lymphocytosis (>5000/μL) and an increased level of lymphocytes (>30%) in the bone marrow. Differential diagnosis is facilitated by immunophenotyping. Other findings related to diagnosis may include hypogammaglobulinemia (<15% of cases) and rarely elevated lactate dehydrogenase. Only 10% of patients have moderate anemia (sometimes immunohemolytic), thrombocytopenia, or both symptoms. A monoclonal serum immunoglobulin spike of the same type can be found on the leukemic cell surface in 2–4% of cases (Tables 12, 13).

Table 12 − **Clinical Staging of Chronic Lymphocytic Leukemia. Rai (United States) Staging System**

	Description
Stage 0	Absolute lymphocytosis: the level of lymphocytes in blood >10,000/μL and ≥30% lymphocytes in the bone marrow
Stage I	Stage 0 plus enlarged lymph nodes
Stage II	Stage 0 plus hepatomegaly or splenomegaly
Stage III	Stage 0 plus anemia with Hb<11 g/dL
Stage IV	Stage 0 plus thrombocytopenia with platelet counts <100,000/μL

Table 13 − **Clinical Staging of Chronic Lymphocytic Leukemia. Binet (Europe) Staging System**

	Describtion
Stage A	Absolute lymphocytosis: the level of lymphocytes in blood >10,000/μL and ≥30% lymphocytes in the bone marrow, Hb ≥10 g/dL, platelets ≥100,000/μL ≤ 2 enlarged areas*
Stage B	As for stage A, but 3–5 enlarged areas*
Stage C	Hb < 10 g/dL, platelets < 100,000/μL, and any number of enlarged areas*
* Enlarged areas: cervical, axillary, inguinal, hepatic, splenic, lymphatic	

Prognosis of CLL

The median survival for patients with B-cell CLL or its complications is 7−10 years. Patients with stages 0, I, II LCC may survive from 5 to 20 years without treatment. Patients with stages III or IV are more likely to die withing 3−4 years after confirmation of the diagnosis. Bone marrow failure is usually associated with short survival. Patients with CLL are more likely to develop a secondary cancer, especially skin cancer.

Treatment of CLL:

- symptom amelioration;
- supportive care.

Although CLL is progressive, some patients may be asymptomatic for years; therapy is not indicated until progression or symptoms occur. Cure usually is not possible, so treatment attempts to ameliorate symptoms and prolong life. Supportive care includes transfusion of packed RBCs or erythropoietin injections for anemia; platelet transfusions for bleeding associated with thrombocytopenia; and antimicrobial drugs for bacterial, fungal, or viral infections. Antibiotic therapy should include bactericidal activities, because patients with neutropenia and agammaglobulinemia are more predisposed to bacterial infections. Therapeutic infusions of γ-globulin should be considered for patients with hypogammaglobulinemia and repeated to prevent or treat refractory infections for prevention as ≥ 2 types of severe infections can develop within 6 months.

Types of specific therapeutic treatment:

- chemotherapy;
- corticosteroids;
- monoclonal antibody therapy;
- radiation therapy;

- these modalities may alleviate symptoms but have not been proven to prolong survival.

Chemotherapy

Chemotherapy is a response to the emergence of symptomatic disease, including constitutional symptoms (e.g., fever, night sweats, extreme fatigue, weight loss); significant hepatomegaly, splenomegaly, or lymphadenopathy; lymphocytosis >100,000/μL; and infections accompanied by anemia, neutropenia, or thrombocytopenia; alkylating agents, especially chlorambucil alone or combined with corticosteroids;

Interferon-α, deoxycoformycin, and 2-chlorodeoxy-adenosine are highly effective in treating hairy cell leukemia.

Corticosteroids

Immunohemolytic anemia and thrombocytopenia are the indications to prescription of corticosteroids. Prednisone 1 mg/kg peroral daily may cause striking, rapid improvement in patients with advanced CLL, although the response to the drug is often short-term. Metabolic complications, increasing rate and severity of infections require long-term use of the drug. Prednisone in combination fludarabine leads to an increased risk for Pneumocystis jiroveci and Listeria infections.

Monoclonal antibody therapy

Rituximab, sold under the brand name Rituxan, is the first monoclonal antibody used in the successful treatment of lymphoid cancers. A partial response rate at conventional doses in patients with CLL is 10 to 15%. In previously untreated patients, the response rate is 75%, with 20% of patients achieving complete remission.

Alemtuzumab, also known as Campath, has response rate of 33% in previously treated patients who were refractory to or

intolerent of their lates chemotherapy.

Fludarabine, also known as Fludara has a response rate of 75 to 80% in previously untreated patients.

Radiation Therapy

Radiotherapy may be given locally to the areas of lymphadenopathy, sometimes with liver and spleen involvement, with good palliative results. Low-dose total body irradiation may also cure cancer or delay its progression.

3.1.3. CHRONIC MYELOID LEUKEMIA (CHRONIC GRANULOCYTIC LEUKEMIA, CHRONIC MYELOGENOUS LEUKEMIA, CHRONIC MYELOCYTIC LEUKEMIA, OR NON-LYMPHOCYTIC LEUKEMIA)

CML occurs when malignant transformation and clonal myeloproliferation of pluripotent stem cell, leading to a striking overproduction of immature granulocytes, take plase.

CML accounts for about 15% of all causes of adult leukemias. CML can strike at any age, though it is uncommon at the age under 10. The average age at diagnosis of CML is 45 to 55 and it may occur in either sex.

Pathophysiology of CML

Most cases of CML induce translocation of the Philadelphia (Ph) chromosome, which is revealed in 95% of patients. It is characterized by a reciprocal translocation of chromosome 9 and 22, t (9; 22) (q34; q11), which results in the fusion of BCR/ABL gene. The BCR/ABL fusion gene is important in the pathogenesis and expression of CML and results in the production of a specific tyrosine kinase. CML ensues when an abnormal pluripotent hematopoietic progenitor cell initiates the excessive production of granulocytes, primarily in the bone

marrow but also at the extramedullary sites (spleen and liver). Although granulocyte production predominates, the neoplastic clone includes RBC, megakaryocyte, monocyte, and even some T and B cells. Normal stem cells are retained and they are able to emerge after medicines suppress the CML clone.

CML has 3 Phases:

- chronic phase is an initial indolent period that lasts from months to years;
- accelerated myeloproliferative phase includes the treatment failure, the worsening anemia, and the progressive thrombocytopenia;
- terminal phase includes the blast crisis, and the blast cell tumors with developmental capacity at the extramedullary sites (such as bones, the central nervous system, lymph nodes, and skin).

Symptoms and Signs of CML

Patients are often asymptomatic on the early stages, with insidious onset of nonspecific symptoms (such as fatigue, weakness, anorexia, weight loss, fever, night sweats, and sense of abdominal fullness). Initially, pallor, bleeding, easy bruising, and lymphadenopathy are unusual, but moderate or suddenly extreme splenomegaly is common (60–70% of cases). With the disease progression, splenomegaly can increase, and pallor and bleeding can occur. Fever, marked lymphadenopathy, and maculopapular skin involvement are ominous developments.

Diagnosis of CML:

- CBC and peripheral blood smear;
- bone marrow examination;
- cytogenetic studies (Ph chromosome);
- CML is diagnosed most frequently by a CBC occasionally or during evaluation of splenomegaly.

Granulocyte count is elevated, usually <50,000/μL in asymptomatic patients and 200,000/μL to 1,000,000/μL in symptomatic patients, and platelet count is normal or moderately increased. Hb level is usually >10 g/dL.

Distinguish CML from Leukocytosis of Other Etiology

In CML, peripheral blood smear shows predominantly immature granulocytes and absolute eosinophilia and basophilia, though in patients with WBC count <50,000/μL, immature granulocytes can be uncommon. Leukocytosis for patients with myelofibrosis is usually associated with nucleated RBCs, tear-shaped RBCs, anemia, and thrombocytopenia. Myeloid leukemoid reactions are the result of cancer or infection; they are not associated with absolute eosinophilia and basophilia

A peripheral blood smear should be taken in the chronic-phase of CML.

The leukocyte alkaline phosphatase score is usually low in CML and increased in leukemoid reactions. Bone marrow examination should be done to evaluate the karyotype as well as cellularity and the degree of myelofibrosis.

The diagnosis is confirmed by the presence of the Ph chromosome in cytogenetic or molecular studies, although it is absent in 5% of patients.

Accelerated phase

During the accelerated phase of the disease, anemia and thrombocytopenia usually develops.

Basophils can increase, and granulocyte maturation process can be defective. The proportion of immature cells and the leukocyte alkaline phosphatase score can increase.

In the bone marrow, myelofibrosis can develop and sideroblasts can be seen in a microscop.

Evolution of the neoplastic clone may be associated with the

development of new abnormal karyotypes, often an extra chromosome 8 or isochromosome 17.

Terminal Phase

Further development of the disease can lead to a blast crisis with the formation of myeloblasts (60% of patients), lymphoblasts (30%), and megakaryocytoblasts (10%).

Additional chromosomal abnormalities frequently occur in 80% of these patients.

In blast-phase CML, the percentage of blasts exceeds 30% in the peripheral blood or in the bone marrow. The blasts have dispersed chromatin, variably prominent nucleoli, and a high nucleus-to-cytoplasm ratio, and they are morphologically indistinguishable from those seen in denovo acute leukemia. There are myeloid, lymphoid, or multilineage phenotype according to the stem-cell nature of CML. Phenotype of blastic transformation is correlated with the secondary cytogenetic abnormalities acquired in the process of transformation. The myeloid phenotype of blasts occurs in about 70–75% of patients, and the leukemic cells in these patients commonly harbor +8, +19, +21, i(17), or (+)Philadelphia chromosome. The lymphoid blast phase is less common and less consistently associated with any particular chromosomal aberrations.

A peripheral blood smear in blast-phase CML is necessary.

Prognosis of CML

With the use of imatinib mesylate (the generic equivalent for Gleevec (R)), >90% of patients survived withing 5 years after the diagnosis. Before treatment with imatinib, from 5% to 10% of patients died within 2 years after the diagnosis; 10–15% died each year thereafter. Median survival was from 4 to 7 years. Most (90%) deaths are due to the blast crisis or the accelerated phase of the disease. Median survival after the blast crisis lasts about 3−6 months, but can to increase up to 12

months with remission.

Ph-negative CML and chronic myelomonocytic leukemia have worse prognosis than Ph-positive CML. Their clinical behavior resembles myelodysplastic syndrome.

Treatment of CML

CML treatment includes:

- a tyrosine kinase inhibitor, sometimes with chemotherapy;
- sometimes, stem cell transplantation.

Treatment is not curative for all situations except for unsuccessful transplantation of stem cells; however, lifetime after the treatment with imatinib can be extended. Imatinib and several new drugs are the inhibitors of the specific tyrosine kinase resulted from the ABL-BCR gene product. It is dramatically effective in achieving complete clinical and cytogenetic remissions of Ph-positive CML, and it is more effective than other regimens (interferon-α-2c and hydroxyurea with or without low-dose cytosine-arabinoside). Imatinib is more effective than other drugs in the accelerated and blast phases.

Old regimens of chemotherapy are reserved for ABL-BCR–negative patients and patients relapsed after receiving imatinib, and patients with blast crisis. The main agents to be used are busulfan (the genetic equivalent for Myleran, hydroxyurea (the genetic equivalent for Hydrea), and interferon-apha. Hydroxyurea is the easiest medicine to manage and has the fewest adverse effects. The starting dosage is generally 500−1000 mg po bid. A complete blood count test should be done every 1−2 weeks, and the dosage should be adjusted accordingly.

Allogenetic stem cell transplantation can be useful for refractory patients after frontline therapy.

Although splenic radiation is rarely used, it is able to be helpful in refractory cases of CML or in terminal patients with

marked splenomegaly. Total dosage usually ranges from 6 Gy to 10 Gy delivered in fractions of 0.25−2 Gy/day.

Splenectomy can alleviate the abdominal discomfort, lessen thrombocytopenia, and relieve transfusion requirements when splenomegaly cannot be controlled by chemotherapy or irradiation. Splenectomy does not play a significant role during the chronic phase of CML.

Multiple Myeloma (Myelomatosis or Plasma Cell Myeloma)

Multiple myeloma is a cancer of plasma cells which produce monoclonal Ig, and they can invade and destroy adjacent bone tissue. Bone pain, renal insufficiency, hypercalcemia, anemia, and recurrent infections belong to common manifestations of the disease.

Diagnosis requires demonstration of M-protein (sometimes present in urine but not serum) and either lytic bone lesions, light-chain proteinuria, or excessive marrow plasma cells. A bone marrow biopsy is usually needed. Specific treatment includes conventional chemotherapy with the medication treatment by bortezomib, lenalidomide, thalidomide, corticosteroids, and high-dose melphalan followed by autologous peripheral blood stem cell transplantation.

The incidence of multiple myeloma is 2 to 4/100,000. The male-female ratio is 1.6:1, and the median age is about 65 years. Prevalence of multiple myeloma in the black race is twice that in whites. The etiology is unknown, although chromosomal and genetic factors, radiation, and chemicals have been suggested.

Pathophysiology

The M-protein produced by the malignant plasma cells is IgG in about 55% of myeloma patients and IgA in about 20%; of patients producing either IgG or IgA; 40% of myeloma patients also have Bence Jones proteinuria, which is free

monoclonal κ or λ light chains in the urine. In 15−20% of patients, plasma cells secrete only Bence Jones protein. IgD myeloma is observed approximately in 1% of cases.

Usually we observe the development of diffuse osteoporosis or discrete osteolytic lesions, in the pelvis, spine, ribs, and skull. Lesions are caused by bone replacement, by expanding plasmacytomas or by cytokines that are secreted by malignant plasma cells which activate osteoclasts and suppress osteoblasts. Although the osteolytic lesions are usually multiple, they occasionally occur as a solitary intramedullary mass. Enhanced bone loss also can lead to hypercalcemia.

Extraosseous solitary plasmacytomas are unusual but can occur in any tissue, especially in the upper respiratory tract. Renal failure (myeloma kidney) occurs in many patients with a diagnosis of multiple myeloma or due to many other causes, most commonly from deposition of light chains in the distal tubules and hypercalcemia (Tab. 15).

Table 15 − **Variants of manifestations of multiple myeloma**

Variants of Manifestations of Multiple Myeloma	
Extramedullary plasmacytoma	Plasmacytomas occur outside the medullary system
Solitary plasmacytoma of the bone	Single bone plasmacytoma, which does not usually produce M-protein
Osteosclerotic myeloma (POEMS syndrome)	Polyneuropathy (chronic inflammatory polyneuropathy) Organomegaly (hepatomegaly, splenomegaly, or lymphadenopathy) Endocrinopathy (e.g., gynecomastia, testicular atrophy) M-protein Skin changes (e.g., hyperpigmentation, excess hair)
Nonsecretory myeloma	Absence of M-protein in serum and urine Presence of M-protein in plasma cells

Along with multiple myeloma we can observe the development of anemia associated with kidney disease or suppression of erythropoiesis by cancer cells. Susceptibility of bacterial infection can occur in some patients. Viral infections, especially herpetic infections, occur more often as a result of increaseingly new treatment modalities. Secondary amyloidosis (see the section Amyloidosis: Secondary amyloidosis) occurs in 10% of patients with myeloma, and most often in patients with λ-type of Bence Jones proteinuria.

Symptoms and Signs

Persistent bone pain (especially in the back or thorax), renal failure, and recurrent bacterial infections are the most common problems that are obvious, but many patients are identified after showing the elevated total protein level in the blood or proteinuria in laboratory routine tests. Pathologic fractures are common, and vertebral collapse can cause the spinal cord compression and paraplegia. Symptoms of anemia predominate or may be the sole reason for determining the disease in some patients; and a few patients have manifestations of hyperviscosity syndrome (see Plasma Cell Disorders: Symptoms and Signs). Peripheral neuropathy, carpal tunnel syndrome, abnormal bleeding, and symptoms of hypercalcemia (eg, polydipsia) are common. Patients with renal failure may also have multiple myeloma. Lymphadenopathy and hepatosplenomegaly are unusual.

Diagnosis:

- CBC with platelets, peripheral blood smear, erythrocyte sedimentation rate, chemistry panel (blood urea nitrogen, creatinine, Ca, uric acid, lactate dehydrogenase);
- serum and urine protein electrophoresis, followed by immunofixation;

- X-rays (skeletal survey);
- bone marrow examination.

Multiple myeloma is suspected in patients >40 years with persistent unexplained bone pain, particularly at night or at rest, other typical symptoms or unexplained laboratory abnormalities such as elevated blood protein or urinary protein, hypercalcemia, renal insufficiency, or anemia. Laboratory evaluation includes routine blood tests, protein electrophoresis, x-rays, and bone marrow examination.

Routine blood tests include the CBC, erythrocyte sedimentation rate, and chemistry panel. Anemia is present in 80% of patients, usually normocytic-normochromic anemia with rouleau formation, which are the clusters of 3 to 12 RBCs in stacks. WBC and platelet counts are usually normal. Erythrocyte sedimentation rate is usually >100 mm/h; blood urea nitrogen, serum creatinine, lactate dehydrogenase, and serum uric acid are often elevated. Anion gap is sometimes low. Hypercalcemia is diagnosed in about 10% of patients.

Protein electrophoresis is done on the serum and urine samples concentrated from a 24-h collection to quantify the urinary M-protein. Serum electrophoresis identifies M-protein in about 80−90% of patients. Free monoclonal light chains (Bence Jones protein) or IgD are determined in 10−20% of patiens. They always have M-protein detected by urine protein electrophoresis. Immunofixation electrophoresis can identify the abnormal Ig, M-protein, and often detects light-chain protein if serum immunoelectrophoresis is falsely negative; immunofixation electrophoresis is done even if serum test is negative and multiple myeloma is strongly suspected. Light-chain analysis with delineation of κ and λ ratios helps to confirm the diagnosis. Light-chain analysis can also be used to follow the efficacy of therapy and provide prognostic data. Serum level of β_2-microglobulin is measured if the diagnosis is either confirmed or very likely to be confirmed; it is often

elevated, and albumin may be decreased. A new international staging system uses the levels of serum albumin and β_2-microglobulin to indicate severity of the disease and a subsequent prognosis.

X-rays include a skeletal survey. Punched-out lytic lesions or diffuse osteoporosis is present in 80% of cases. Radionuclide bone scans usually are not helpful. Magnetic resonance imaging can provide more details and it is obtained if specific sites of pain or neurologic symptoms are present.

Bone marrow aspiration and biopsy are done and reveal sheets or clusters of plasma cells; myeloma is diagnosed when >10% of the cells are of the myeloma type. However, marrow involvement is patchy; therefore, some samples from patients with myeloma may show <10% of plasma cells. Still, the number of marrow plasma cells is rarely normal. Plasma cell morphology does not correlate with the class of immunoglobulin synthesized. Chromosomal studies on bone marrow may reveal specific karyotypic abnormalities in plasma cells associated with differences in their survival.

In patients without serum M protein, myeloma is indicated by Bence Jones proteinuria >300 mg/24 h, osteolytic lesions (without evidence of metastatic cancer or granulomatous disease), and sheets or clusters of marrow plasma cells.

Prognosis

The disease is progressive and incurable, but median survival has recently improved to >5 years as a result of advances in treatment. Signs of unfavorable prognosis when diagnosing are expressed by lower serum albumin and higher β_2-microglobulin levels. Patients with renal failure also have poorly prognosis unless kidney function is improved with therapy.

Since multiple myeloma is ultimately fatal, patients should discuss about end-of-life care with their doctors, family, and

friends. Points for discussion should be about advance directives, the use of feeding tubes, and pain relief.

Treatment:

- chemotherapy for symptomatic patients
- thalidomide (trade name: Thalomid), bortezomib (trade name: Velcade), or lenalidomide with corticosteroids and/or chemotherapy;
- possible maintenance therapy;
- possible stem cell transplantation;
- possible radiation therapy;
- treatment of complications (anemia, hypercalcemia, renal insufficiency, infections, skeletal lesions).

Treatment of myeloma has improved in the past decade, and long-term survival is a reasonable therapeutic target. Therapy involves the direct treatment of malignant cells for symptomatic patients and the treatment of complications. Probably the benefits of treatment are absent for asymptomatic patients, which is usually withheld until symptoms or complications develop. However, patients with lytic lesions or bone tissue loss (osteopenia or osteoporosis) should be treated with monthly infusions of zoledronic acid, called zometa, to reduce the risk of skeletal complications.

Treatment of malignant cells: Until recently, conventional chemotherapy consisted only of oral melphalan and prednisone intake in cycles of 4 to 6 weeks with evaluation of response during months. Recent studies show superior outcome with the addition of either bortezomib or thalidomide. Other chemotherapeutic drugs, including alkylating medicines (e.g., cyclophosphamide, named Cytoxan; doxorubicin, named Adriamycin, and its newer analog pegylated liposomal doxorubicin, are also more effective in combination with thalidomide or bortezomib. A lot of other patients are

effectively treated by bortezomib, thalidomide, or lenalidomide in combination with glucocorticoids and/or chemotherapy.

Chemotherapy response is indicated by decreases in serum or urine M-protein, increases in RBCs, and improvement in renal function in patients with kidney failure.

Autologous peripheral blood stem cell transplantation may be considered for patients with adequate cardiac, hepatic, pulmonary, and renal functions, particularly for persons with stable disease or responsive one after several cycles of initial therapy. Allogeneic stem cell transplantation after non-myeloablative chemotherapy (e.g., low-dose cyclophosphamide and fludarabine or low-dose radiation therapy) can provide myeloma-free survival of 5 to 10 years in some patients. However, allogeneic stem cell transplantation remains an experimental approach in treatment because of high morbidity and mortality from graft vs. host disease.

In relapsed or refractory myeloma, combinations of bortezomib, thalidomide, or its newer analog lenalidomide with chemotherapy or corticosteroids may be used. These drugs are usually combined with other effective drugs that the patient has not yet been treated with, although patients with prolonged remissions may respond to retreatment with the same regimen that led to the remission.

Maintenance therapy has been tried with nonchemotherapeutic drugs, including interferon-α, which prolongs remission but does not improve survival and is associated with significant adverse effects. Following a response to corticosteroid-based regimens, corticosteroids alone are effective as a maintenance treatment. Thalidomide may also be effective as a maintenance treatment, and studies are evaluating maintenance therapy with bortezomib and lenalidomide among patients with responsivity to these drugs prescribed alone or in combination therapeutic regimens.

Treatment of complications: In addition to treatment of malignant cells, therapy must also be directed at complications such as anemia, hypercalcemia, renal insufficiency, infections, and skeletal lesions.

Anemia can be treated with recombinant erythropoietin (40,000 units sc q wk) in patients whose anemia is inadequately relieved by chemotherapy. If there are cardiovascular or significant systemic symptoms after anemia, packed RBCs are transfused. Plasmapheresis is indicated if there is the development of hyperviscosity (see Plasma Cell Disorders: Symptoms and Signs).

Hypercalcemia is treated by saluresis, IV bisphosphonates, and sometimes with Prednisone. Most patients do not require Allopurinol. However, Allopurinol is prescribed for patients with high levels of serum uric acid or high tumor burden and a high risk of tumor lysis syndrome after treatment.

Renal compromise can be improved by adequate hydration. Even patients with prolonged, massive Bence Jones proteinuria (≥10−30 g/day) can have intact renal function if they maintain urine output >2000 mL/day. Acute oliguric renal failure in patients with Bence Jones proteinuria may be caused by the combination of dehydration and high osmolar contrast media i.v.

The infection is more likely to happen during chemotherapy-induced neutropenia. In addition, infections with herpes zoster virus occur more frequently in patients treated with new antimyeloma drugs. Documented bacterial infections should be treated with antibiotics; however, preventive use of antibiotics is not routinely recommended. Preventive use of antiviral drugs may be indicated for patients who receive specific drugs. Preventive IV Ig can reduce the risk of infection, but it is commonly reserved for patients with recurring infections. Pneumococcal and influenza vaccines are indicated to prevent the infection.

Skeletal lesions require multiple supportive measures. Prescription of ambulation and supplemental Ca and vitamin D helps to preserve the density of bones. Analgesics and palliative doses of radiation therapy (18−24 Gy) can alleviate bone pain. However, radiation therapy is prescribed to impaire the patient's ability for receiving the cytotoxic doses of systemic chemotherapy. Receiving a monthly i.v. bisphosphonates (either Pamidronate or zoledronic acid) is necessary for patients, especially with lytic lesions and generalized osteoporosis or osteopenia. Skeletal complications and bone pain are reduced by bisphosphonates with antitumor effect.

Introduction (Dysproteinemias. Monoclonal Gammopathies. Paraproteinemias. Plasma Cell Dyscrasias)

Plasma cell disorders are the diverse group of disorders with unknown etiology characterized by the disproportionate proliferation of one clone of B cells and the presence of a structurally and electrophoretically homogeneous (monoclonal) Ig or polypeptide subunit in serum, urine, or both.

Pathophysiology

For structural features and classification of the Ig, see Biology of the Immune System: Antibodies.

After the development in the bone marrow, undifferentiated B cells enter the peripheral lymphoid tissues, such as lymph nodes, the spleen, the gut, and Peyer's patches. Here, they begin to differentiate into cells, each being able to respond the limited number of antigens. There is a clonal proliferation of some B cells into plasma cells after connection with the appropriate antigen. Each clonal plasma cell line is committed to synthesize one specific Ig antibody that consists of 2 identical heavy chains (gamma [γ], mu [μ], alpha [α], delta [δ],

or epsilon [ε]) and 2 identical light chains (kappa [κ] or lambda [λ]). A slight excess of light chains is normally produced, and urinary excretion of small amounts of free polyclonal light chains (≤40 mg/24 h) is normal.

The etiology of plasma cell disorders is unknown and they are characterized by the disproportionate proliferation of one clone. The result is a corresponding increase in the serum level of its product, the monoclonal Ig protein (M-protein).

M-proteins may consist of both heavy and light chains or of only one type of chain. Some of them show the antibody's activity with ability to produce an autoimmune damage of organs, particularly kidneys. When M-proteins are produced, production of other Ig is commonly reduced, and immunity may become impaired. M-protein can cover the platelets, inactivate clotting factors, increase blood viscosity, and cause bleeding. M-proteins can also produce secondary amyloidosis. The clonal cells can infiltrate bone matrix or marrow, with the resultant osteoporosis, hypercalcemia, anemia, or pancytopenia.

Plasma cell disorders may vary from asymptomatic, stable conditions (in which only protein is present) to progressive cancers (e.g., multiple myeloma: to classify plasma cell disorders, see Table 1). Sometimes, transient plasma cell disorders are typical for patients with drug hypersensitivity (sulfonamide, phenytoin and penicillin), with presumed viral infections, and after cardiac or transplant surgery.

Plasma cell disorders may be suspected because of clinical manifestations, findings during evaluation of anemia, or an incidental finding of elevated serum protein or proteinuria that caused further evaluation with serum or urine protein electrophoresis. There is a way of determining M-protein, which is further evaluated by immunofixation electrophoresis to identify heavy and light chain classes.

Macroglobulinemia (Primary Macroglobulinemia. Waldenström's Macroglobulinemia)

Macroglobulinemia is a malignant plasma cell disorder which causes the production of excessive amounts of IgM M-proteins by B cells. The disease manifests itself in hyperviscosity, bleeding, recurring infections, and generalized adenopathy. Diagnosis requires bone marrow examination and demonstration of M-protein. Treatment includes plasmapheresis as needed for hyperviscosity, and systemic therapy with alkylating drugs, corticosteroids, nucleoside analogs, or monoclonal antibodies.

Macroglobulinemia, an uncommon B-cell cancer, is clinically more similar to a lymphomatous disease than to myeloma and other plasma cell disorders. The cause is unknown. Men are affected more often than women; the median age is 65.

Macroglobulinemia is the second most common malignant disorder associated with a monoclonal gammopathy after myeloma. Excessive amounts of IgM M-proteins can also accumulate in other disorders and cause manifestations similar to macroglobulinemia. Small monoclonal IgM components are present in the serum of about 5% of patients with B-cell non-Hodgkin lymphoma; this circumstance is termed macroglobulinemic lymphoma. Moreover, IgM M-proteins are occasionally present in patients with chronic lymphocytic leukemia or other lymphoproliferative disorders.

Clinical manifestations of macroglobulinemia may be caused by a large amount of high molecular weight monoclonal IgM proteins circulated in plasma, but most patients do not have problems related to high IgM levels. Some of these proteins are antibodies directed toward autologous IgG (rheumatoid factors) or I antigens (cold agglutinins). About

10% of them are cryoglobulins. Secondary amyloidosis occurs in 5% of patients.

Symptoms and Signs

Most patients have asymptomatic disease, but many patients have signs of hyperviscosity syndrome, including fatigue, weakness, skin and mucosal bleeding, visual disturbances, headache, symptoms of peripheral neuropathy, and other neurologic manifestations. An increased plasma volume can precipitate the heart failure. Cold sensitivity, Raynaud's syndrome, or recurring bacterial infections may appear.

A complete examination can reveal lymphadenopathy, hepatosplenomegaly, and purpura. Marked engorgement and localized narrowing of retinal veins, which resemble sausage links, suggests hyperviscosity syndrome. Retinal hemorrhages, exudates, microaneurysms, and papilledema appear in the late stages.

Diagnosis:

- CBC with platelets, RBC indices, peripheral blood smear;
- serum protein electrophoresis, followed by serum and urine immunofixation;
- serum viscosity assay;
- bone marrow examination;
- sometimes, lymph node biopsy.

Macroglobulinemia is suspected in patients with symptoms of hyperviscosity or other typical symptoms, particularly, if anemia is present. However, it is often diagnosed accidentally, when protein electrophoresis reveals M-protein that proves to be IgM by immunofixation. The laboratory examination includes tests to evaluate plasma cell disorders (see Plasma Cell Disorders: Multiple Myeloma) as well as measurement of

cryoglobulins, rheumatoid factor, cold agglutinins, coagulation studies, and the direct Coombs test.

A moderate normocytic normochromic anemia, marked rouleaux formation, and a very high erythrocyte sedimentation rate are typical. Leukopenia, relative lymphocytosis, and thrombocytopenia occur occasionally. Cryoglobulins, rheumatoid factor, or cold agglutinins may be present. If cold agglutinins are present, the direct Coombs test is usually positive. The appearance of various coagulation and platelet function abnormalities is possible. Results of routine blood studies may be spurious if cryoglobulinemia or marked hyperviscosity are present. Normal Ig are decreased in half of patients.

Immunofixation electrophoresis of concentrated urine often shows a monoclonal light chain (usually κ), but gross Bence Jones proteinuria is unusual. Bone marrow studies show a variable increase of plasma cells, lymphocytes, plasmacytoid lymphocytes, and mast cells. Periodic acid-Schiff-positive material may be present in lymphoid cells. Lymph node biopsy, done if bone marrow examination is normal, is frequently interpreted as a diffuse well-differentiated or plasmacytic lymphocytic lymphoma. Serum viscosity is measured to confirm of suspected hyperviscosity, and when > 4.0 (normal, 1.4 to 1.8) is usually present.

Treatment:

- plasmapheresis (when hyperviscosity is present);
- alkylating drugs, nucleoside analogues, monoclonal antibodies (Rituximab), or their combination;
- possible use of Bortezomib, Thalidomide, or Lenalidomide;
- the course is variable, with the median survival of patients from 7 to 10 years. The age is more than 60 years; anemia and cryoglobulinemia are precursors of a smaller survival rate.

Often, the patients are not treated for many years. If they have hyperviscosity, the initial treatment includes plasmapheresis, with rapid reverse of bleeding as well as neurologic abnormalities. Plasmapheresis must be repeated.

Long-term treatment with oral alkylating drugs may be indicated for palliation, but bone marrow toxicity can occur. Nucleoside analogs (Fludarabine and 2-Chlorodeoxyadenosine) are response products in large numbers in newly diagnosed patients. Rituximab can reduce tumor burden without suppressing normal hematopoiesis. However, during the first several months, IgM levels may increase, requiring plasmapheresis. The proteasome inhibitor, called Bortezomib, and the immunomodulating agents Thalidomide and Lenalidomide are also effective against this cancer.

Syndrome of Disseminated Intravascular Coagulation (DIC)

DIC is one of the most common acquired coagulopathies. It belongs to a leading contributor in the pathogenesis of some diseases. DIC can complicate various pathological processes, and it is often the cause of an immediate death. DIC may occurre in any doctor's clinical practice of all specialties, but it is often not diagnosed or diagnosed too late.

It appears as a result of involvement of a lot of factors in the pathological process, which activates coagulation and platelet aggregation with the subsequent generalized formation of microclots and microcirculation disorders in organs and tissues, which reduce the extreme degenerative changes. Hypocoagulation, thrombocytopenia and bleeding, caused by consumption coagulopathy, develop simultaneously with the fibrin-embolism.

Etiology

There are such forms of DIC according to their cause of development:

- infectional and septic (occur in septic conditions and generalized infection);
- posttraumatic (occurs during crash syndrome or burn disease, multiple bone fractures);
- shock-producing (various types of shock);
- surgical (after operations with large tissue trauma);
- obstetric (premature detachment of placenta, supply of amniotic fluid into the blood, septic abortion, severy course of toxicosis and pyelonephritis in pregnant women);
- toxigenic (after snake bite);
- tumor (as a result of malignant tumor growth, especially hemoblastosis;
- allergic (as a result of immune and immunocomplex diseases)
- caused by massive blood transfusion and transfusion of incompatible blood;
- caused by destructive processes in the liver, pancreas, and kidneys;
- caused by systemic diseases of connective tissue and other immunocomplex diseases (glomerulonephritis, etc.).

Pathogenesis

Pathogenesis of DIC is based on "a humoral explosion of proteases", which is a simultaneous activation of all plasma proteolytic enzymes that belong to the four extracellular biochemical systems:

1. Blood clotting system
2. Fibrinolytic system
3. Kallikrein-kinin system
4. System of complement.

The formation of active proteolytic blood enzymes has such peculiarities as:

- possible autoactivation of enzymes means that active enzyme converts inactive form into an active one by acting on an inactive form;
- activation of active proteases by other active proteases (cross-activation);
- chain character of the activation reaction. In theory, the presence of only one molecule of active protease can activate the residue of proteases in the blood. However, a proteolytic activation is limited in healthy people and is associated with the presence of a large group of protease inhibitors. Chain character of the reaction activating the proteolytic systems in blood plasma is associated with insufficient production of protease inhibitors to neutralize a large number of active proteases, entering the blood. Such an activation of a general nature involves all the blood proteases and is called "humoral protease explosion".

There are three main sources of proteases in the blood:

1. The acute damage to a large number of cells which stimulates the entering of lysosomal proteases and tissue thromboplastin into the blood.

2. The entering of a large number of extracellular proteases into the blood (e.g., trypsin during acute pancreatitis and enzymes of amniotic fluid).

3. The entering of exogenous proteases of bacterial cells into the blood in patients with sepsis and poisonous snakes.

There are two phases of pathogenesis of DIC:

Phase I is called the phase of hypercoagulation and platelet aggregation. This phase is based on the total activation of the coagulation system, i.e, thrombin generation which leads to

fibrin clot formation and platelet aggregation. There are the following starting mechanisms for this phase:

- enzymatic mechanism, associated with the entering of a large number of active proteases and tissue thromboplastin into the blood;
- contact mechanism, associated with the activation of XII coagulation factor during its contact with the foreign body surfaces (extracorporeal dialysis, hemodialysis, artificial heart valves);
- platelet mechanism, associated with the primary activation of platelet aggregation during total endothelial damage to blood vessels, abnormal blood rheology, and acute intravascular hemolysis of erythrocytes.

The result of these mechanisms realization is the formation of a large number of micro clots and aggregates of cells, with subsequent microcirculation disorders and sludge syndrome development.

Phase II is the phase of hypocoagulation (hemorrhagic syndrome). This phase is the result of mechanism's depletion of vascular-platelet and coagulation homeostasis. It is characterized by the following important factors:

- reduction of blood coagulation activity (factors II, V, VIII);
- activation of the fibrinolytic system (by derecting a flow of a large number of fibrinolysis activators into the blood);
- increased anticoagulation activity due to the formation of fibrinolysis blood products;
- development of the consumption thrombocytopenia;
- increase vascular permeability of vascular (as a result of the formation a large number of kinins).

Classifications:

1. According to the ICD – 10 International Classification of Diseases: the disease code 65 D.

2. Classification by V. G. Lychova (1998):

1) according to the etiology (septic, obstetric, traumatic, immunocomplex, etc.);

2) according to the course of the disease (immediate, acute, subacute, chronic, recurrent, and latent);

3) according to stages (phases):

- stage I is the stage of hypercoagulation and platelet aggregation;
- stage II is the intermediat phase of increased coagulopathy and thrombocytopenia, multidirectional shifts in coagulation tests;
- stage III is the phase of deep hypocoagulation (complete absence of coagulation);
- renovation (during a mild course of the complication phase).

3. Clinical and pathogenetic variants:

1) strong predominance of fibrinolysis and hemorrhagic syndrome;

2) strong manifestation of coagulation, depressed fibrinolysis and symptoms of venouse thrombosis and thromboembolism;

3) acute dysfunctions of internal organs on the background of moderate hemorrhages with activation of coagulation and weakened anticoagulation;

4) predominant activation of cellular hemostasis, peripheral blood sequestration with the blockage of microcirculation, decrease in blood pressure and circulating blood volume;

5) predominant activation of hemostasis system by immune complexes, cryoglobulins, and toxins in capillaries lesions, microvascular thrombohemorrhages, and skin necrosis on the background of bleeding.

Clinical course

Acute period of DIC lasts hours, rarely − days. It is a result of shocks of different etiologies, prenatal waters embolism,

premature separation of placenta, acute intravascular hemolysis, complications after surgical operations with extracorporeal circulation, septicemia, and many other pathological processes.

Subacute period of DIC lasts days, weeks, and months. It is observed after malignant tumors, myeloid leucosis, especially acute promyelocyte leucosis, kollagenozes, allergic vasculitis, amyloidosis, liver cirrhosis, uremia, viral and bacterial infections, and intrauterine fetal death in obstetric practice.

Chronic period of DIC lasts months and years. It is observed in giant hemangioma (Kasabah-Meryta syndrome), massive cavernosus degeneration of blood vessels (e.g., portal system), etc. There are no symptoms with the latent form. It can be diagnosed only by laboratory tests.

The clinical forms of DIC are defined schematically because of their transition. For example, the latent form with long duration can be converted into an acute form.

The clinical picture depends mainly on the course of the main disease and the course of DIC. The phase of hypercoagulation is characterized by sudden coagulation or mixed shock, collapse, and an acute decrease in arterial and central venous pressures. There are also symptoms of the main disease. The blockage of pulmonary capillaries is the cause of dyspnea (called "shock lung"). The death can be caused by acute pulmonary heart in the most difficult cases. The damage to the central nervous system is characterized by intermittent convulsions, symptoms of small-throat encephalopathy and coma. The duration of this phase is different for different diseases. It is short for obstetrical and surgical diseases, longer − for therapeutic illnesses, and latent − for shocks. There is no clinical manifestation of hypercoagulation phase in the last two cases.

The phase of hypocoagulation with different severity of hemorrhagic syndrome becomes after the phase of

hypercoagulation. Phase I is often invisible: there is only hemorrhagic syndrome, complicated by a particular process or a disease. Hemorrhagic syndrome is characterized by different kinds of hemorrhages, ecchymosis, and large hematomas, or bleeding at the sites of palpation. There is also bleeding from mucous membranes (of the nose, uterine, and gums). A severe course is characterized by generalized massive hemorrhage, renal hemorrhage, bleeding from the digestive tract, bleeding in the internal organs and in the central nervous system, profuse bleeding from the genital system after delivery, and bleeding from operative injury and stitches after surgical operation.

The acute posthemorrhagic anemia with loss of blood is developed as a result of bleeding. Its severity depends on the amount of the lost blood. The symptoms of hypovolemia and metabolic disorders are also expressed. There is the transformation of coagulation shock into hemorrhagic shock.

Further more, there is the development of anatomical and functional disorders in organs and systems such as acute insufficiency of adrenalglands, parenchymal dystrophy of the liver, liver and spleen insufficiency, small-throat encephalopathy as a result of fibrin embolism and blockage of microcirculation. Such changes appear in kidneys, even when DIC syndrome is mild. Oliguria and mild azotemia are developing. Massive DIC syndrome is characterized by necrosis and uremia.

Hemorrhages and necroses are focused in the area of occlusive vessels. Ulcers are determined in digestive tract. In some cases, blood clots of fibrin can be detected only when examined by microscope. We can see them with the help of specific fixation and coloration. The absence of clots does not deny DIC syndrome, because they can be dissolved by secondary fibrinolysis or proteolytic leukocytic enzymes.

The clinics of subacute and chronic forms of DIC syndrome differ from that one of an acute form. The symptoms of the

basic disease appear first. The variability of clinical manifestations depends on the main disease.

The general condition of the patient deteriorates rapidly. The collapse and hemorrhages on the skin are common manifestations. Such course of DIC syndrome is observed in other diseases. Thrombosis and thrombophlebitis are clinical characteristics of other diseases such as malignant tumors. It can be the single symptom of DIC syndrome for a long time. In these cases the bleeding of different intensity is the clinical manifestation of the hypocoagulation phase. The bleeding after tooth extraction or surgical operation is common.

The chronic forms can be characterized by the latent course of the disease. The use of procoagulative medicines for intravascular coagulation is compensated by their increased synthesis in such cases.

Laboratory diagnosis. The laboratory diagnosis of DIC syndrome is difficult to establish because the results of research depend on the form, stage, and severity of the disease, time of investigations, and the stage of disorders in coagulate hemostasis.

The acute period. There is the decrease in time of blood coagulation, partial time of tromboplastin, time of recalcification of plasma, time of heparin in blood analysis for hypercoagulation because of trombinemia. The signs of hypercoagulation are defined. According to the results of thromboelastography, the presence of chronometric and structural blood hypercoagulation and the increase in adhesion and aggregation for platelets are determined. The activation of the fibrinolysis system, the products of fibrin degradation products (FDP_s), positive tests with ethanol and protamine sulfate are determined. The quantity of platelets and antithrombin III is decreased. Sometimes the collection of blood is impossible because of coagulation in the needle.

Hypocoagulation is the next phase after hypercoagulation. The multidirectional general coagulation tests and thrombocytopenia are defined in transitional period. The blood clot (Lee-White sample) can appear quickly and timely, but it is small and reacts quickly in hypofibrinogenemia. The time of blood coagulation, recalcification of plasma and heparin is increased. This is hypocoagulation. The significant increase of prothrombin time is common for DIC syndrome. The prothrombin time of plasma is increased as a result of using factors of prothrombin complex. Thrombocytopenia is the constant attribute of DIC-syndrome. The reduction of the content of fibrinogen and other procoagulants (called thrombocytopenia and coagulopathy after consumption) is possible. The characteristic of this phase are rapid fibrinolysis, FDP_s, soluble complexes of fibrin-monomers, positive tests with ethanol and protamine sulfate. There is determined blocked fibrinogen in the serum with the help of ephah-poison (serum coagulation test with ephah-poison) and the positive test of adhesion for staphylococcus. There is the decrease in the levels of antithrombin III and plasminogen in serum as a result of exhaustion of physiological anticoagulants and components of fibrinolitic system. The morphologically changed erythrocytes, microspherocytosis, shizocytosis (the characteristic signs of DIC) are determined in the blood smear. The blood is not coagulated even after addition of thrombin in severe cases.

The Lee-White sample is used in urgent cases (especially in obstetrics) to confirm hypocoagulation phase if the main laboratory is not available. It is necessary to take 3−4 ml of blood in the test-tube and put it into water bath. The temperature should be +37°C. The blood from birth canal is not used. Normally the compact clot is defined in 5−9 minutes. The clot is formed in a timely manner in hypofibrinogenemia, but it is small, soft and soluble for strong fibrinolysis with quickly

reaction. There is no coagulation of blood during full blockage of fibrinogen. The absence of blood coagulation after thrombin addition is the direct confirmation of the diagnosis.

Subacute course. The characteristic sign of subacute course of DIC syndrome is the gradual increase of coagulation disorders (days and months). The informative coagulation tests for acute and subacute periods are similar.

The long coagulation, clinically characterized by thromboembolia, is possible for weak course of DIC-syndrome. The laboratory data at this stage are the reduced rates of all coagulation tests, high sudden aggregation of thrombocytes, accelerated fibrinolysis, high levels of FDP_s, and positive tests of coagulation. At this stage, there are the development of significant hypocoagulation and changes, characterized by consumption coagulopathy such as reduced level of fibrinogen and other procoagulation drugs, increased level of FDP_s, positive tests with ethanol and protamine sulfate, positive serum coagulation sample with ephah-poison, and adhesion for staphylococcus. Antitrombin 3 level is decreased. Shizocytes are defined in the peripheral blood smear.

The course of chronic disease lasts months and years. Sometimes the level of fibrinogen, factors of prothrombin complex and other procoagulation substances, and number of thrombocytes are normal or even increased for latent and chronic forms of DIC syndrome, which is a result of hyperproduction of these components after theit large consumption. The laboratory confirms DIC syndrome by detection of FDP_s, fibrin-monomers and dicrease in the half-fragmentation period of fibrinogen (1−2 days; normal duration is 4 days).

The diagnostic standards: V. A. Likhachev (1993−1998) developed a diagnostic algorithm of DIC. All symptoms of illness are grouped in three classes, presented in Table 15: Class A (initial clinical situation, factors and pathology); Class

B (the most typical clinical symptoms of DIC); Class C (laboratory indicators).

Table 15 – **Comon signs and symptoms of DIC. Class A**

Group number	**Initial clinical situation**	**Measure of trust**
1	- all types of shock: stages II-III; - HUS; - sepsis; - acute intravascular hemolysis; - massive pulmonary embolism; - acute hepato-renal insufficiency; - crush-syndrome; - burns: stages II-III (burns >35% of the body); - amniotic fluid embolism; - acute promyelocytic leukemia; - severe intoxication by snake's poison; - massive destruction of organs;	0.95
2	- hemorrhagic necrotizing pancreatitis; - pulmonary gangrene due to Staphylococcus aureus; - eclampsia; - other types of obstetric pathology; - infant respiratory distress syndrome; - drug-induced necrotic purpura; - intensive hemolysis; -heart insufficiency and combined insufficiency of heart and lungs with intensive development; - severe forms of radiation and cytostatic disease;	0.8

Table 15 (cont.)

Group number	Initial clinical situation	Measure of trust
3	- hemoblastosis; - malignant tumors; - postoperative traumas of glandular and parenchymal organs; - fractures of bones and politrauma; - 2nd and 3rd degree burns and frostbite (<35% of the body); - placenta abruption, intrauterine fetal death; - cystic mole; - infectiousl and toxic diseases; - system vasculitis; - macrofocal myocardial heart attack; (excluding severe cardiogenic shock); - congestive heart failure; - Kasabach-Merritt syndrome;	0.7
4	- other pathological processes which are not included in the groups № 1−3. But the measure of trust can increase in the group № 4 if there is the combination with the groups № 2 or № 3	0.30–0.50
	Clinical signs - acute respiratory, adrenal insufficiencies or renal failure; - combined insufficiency of two and more of organs described above; - local bleeding; - multiple hemorrhages of different localization; - local thrombosis or heart attack; - the combination of thrombosis (heart attack) with bleeding;	 0.60 0.95 0.40 0.72 0.35 0.90

Table 15 (cont.)

Group number	Initial clinical situation	Measure of trust
	- collapse; - lasting recurrent shock, with hemorrhages; - other symptoms; - absence of clinical symptoms	0.55 0.95 0.20 0.10

Every symptom has a corresponding measure of trust, experimentally calculated by Shortlif's formula (from 0 to 1) (Tab. 16).

Table 16 **– Common Signs of DIC: Class C**

Laboratory tests	Measure of trust
- the number of platelets in the blood $<130 \times 10^9$/l or $>450 \times 10^9$/l;	0.50
- hypo- or hypercoagulation (PT>20 s or <14 s, thrombin time >16 or <14 s, APTT >45 or <35 s;	0.85
- multidirectional indicators of coagulation tests (PT, APTT);	0.85
- the absence of blood coagulation according to the Lee-White test;	0.95
- increased content of plasma soluble fibrin-monomeric complexes and FDP_s;	0.78
- reduced levels of antithrombin III to <70 %;	0.50
- raised plasma concentration of platelet factor 4 (PF-4) or β-trombohlobulin (labialization of platelets);	0.70
- damage to erythrocytes (light fraction of erythrocytes in verografin sodium solution in the blood).	0.80

The possibility of DIC is calculated by the formula of V. G. Lykhachev, 1998:

The sum of the characteristics of classes A and B (or X_0) =
= MD (A) + MD(B) · (1-MD(A));
$MD_{gen} = X_0 + (1 – X_0) \cdot MD(C)$.

The risk of developing DIC is the highest for highest levels of MD_{gen}.

The differential diagnosis of DIC is made with congenital afibrinogenemia, hypofibrinogenemia caused by serious disorders in liver's parenchyma and primary fibrinolysis. Anamnesis and laboratory analysis are very important for diagnosis of two primary forms. It is necessary to remember that liver diseases are often complicated by DIC. The number of platelets does not reduce in hereditary hypo- and afibrinogenemia and hereditary hyperfibrinolysis.

Principles of treatment

The treatment regimen depends on the disease severity.
The therapeutic diet is table №15.
Medical treatment: The treatment of DIC depends mainly on its cause, forms, and stages.

The first stage of treatment is to liquidate cause of the diseases assosiated with DIC such as obstetric complications, massive antibiotic therapy of sepsis, surgical treatment of tumors, etc.

The treatment of shock (treatment of acute DIC):
- infusion of blood substitutes (salt solutions, Rheopolyglucin, and albumin) with high doses of glucocorticoids (hydrocortisone 1000−1500 mg/day; prednisolone 60 mg/day; dexamethasone 150−200 mg/day). The daily dose of glucocorticoids can be taken at once in severe cases (pulse therapy).

N.B. The introduction of anticoagulants eliminates the action of glucocorticoids associated with stimulation of blood coagulation;

- the infusion of 1 ml of 0.2% solution of norepinephrine together with 500 ml of isotonic solution or Ringer's solution with the rate of 10−15 drops per minute is indicated only in case of anaphylactic and/or exotoxic shock; in other cases, preference is given to dopamin (dopamine)- biological precursor of norepinephrine. 200 mg (5 ml) dopamine are dissolved in 400 ml of Rheopolyglucin or 5% glucose solution, administered intravenously with an initial rate of 2−4 mcg/kg/min with a gradual increase up to 10 mcg/kg/min. Dopamine delates blood vessels of the kidneys, stimulates the contractility of the myocardium, increases blood pressure. It does not increase coagulation and platelet aggregation such as norepinephrine.

Heparin is a drug of choice with anticoagulant effect, associated with activation of such natural anticoagulant as antithrombin III, in the hypercoagulation phase and chronic form of DIC. If the content of antithrombin III is reduced − heparin will not be effective. The large doses of heparin lead to a rapid depletion of antithrombin III, which is a result of rebound hypercoagulation. Therefore, we should use heparin with drugs that include antithrombin III (fresh frozen or fresh native plasma). Heparin is quickly outputted for intravenous infusion; therefore, it is recommended to use the technique of infusion through the pump with constant rate during the day or by subcutaneous injection in the abdomen 3−4 times a day (half-life is extended on account of prolonged absorption from the subcutaneous depot). The most common are such methods of introduction of heparin:

- firstly we use intravenous bolus of 10,000 IU, then 1000−500 IU per hour drip up to 20,000 IU per day;

- firstly we use intravenous bolus of 10,000 IU, then − under the skin of the abdomen 5000 IU every 6−8 hours.

Remember:

Heparin can increase thrombocytopenia, which is associated with a decrease of functionally active platelets in the blood flow. Careful monitoring of blood platelets during heparin therapy is necessary.

One of the main methods of DIC treatment at all its stages is administration of fresh frozen plasma (from one group). The fresh frozen plasma is slowly warmed to 37 °C; bolus is injected at a dose of 600−800 ml, and then every 6−8 h at a dose of 300−400 ml. Fresh frozen plasma contains all the necessary components for correction of hemostasis disorders (procoagulant, antithrombin III, protein C, components of the fibrinolytic system, physiological antiplatelet agents). Transfusion of cryoplasma helps to restore antiproteinase activity and to compensate the volume of the circulation fluid. If cryoplasma is not available, we should inject fresh plasma, but its effectiveness is lower. We should start to infuse plasma during the phase of hypercoagulation. It is combined with heparin, which is prescribed before each infusion of plasma intravenously, 2500−5000 IU (the dose is 5000–7500 IU for severe hypercoagulation) to activate antithrombin III. In this case heparin can be entered directly into the vial of plasma. The slow infusion of cryoplasma is not effective.

The early administration of the following drugs to improve microcirculation is very important: curantyl (0.1 g 3 times a day orally), trental (0.1 g in 250−500 ml of 5% glucose solution intravenously for 1.5−2 hours) without expressed atherosclerosis, and ticlid (0.3 g 3 times a day orally). The prescription of acetylsalicylic acid is not advisable because of the risk of severe gastrointestinal bleeding.

The treatment of DIC in the intermediate phase and in the phase of hypercoagulation is the same, but the dose of heparin may be reduced according with the indicators of coagulation.

The use of heparin is not recommended in phase of hypocoagulation, severe thrombocytopenia and bleeding, but some physicians prescribe small doses of heparin (2,500 IU) before blood or plasma transfusion in this case.

Firstly, drugs to reduce the blockage of the microcirculation such as rheopolyglucin, dipyridamole, aminophylline, and papaverine are prescribed. We should administer cryoplasma as soon as possible. At the same time we should prescribe drugs to eliminate of all types of proteolysis – broad-spectrum protease inhibitors (trasylol, contrycal and others). These drugs inhibit fibrinolysis and other types of proteolysis, and also activate the kallikrein-kinin system, not stabilizing fibrin in microcirculation. They are prescribed in high doses. Therefore, contrycal is administered intravenously at a dose of 50,000−100,000 IU. Then injection of the drug is repeated and its daily dose can be increased up to 500,000 IU and more. In some literature, there are recommendations to administer aminocapronic acid. However, aminocaproic acid inhibits only fibrinolysis, not affecting other types of proteolysis. Aminocaproic acid stimulates the blokage of fibrin in small vessels. Furthermore, fibrin is not exposed to fibrinolysis. As a result it causes serious damages in parenchymal organs. Therefore, the administration of aminocaproic acid in DIC is questionable.

Due to the fact that the main drugs for therapy of DIC (cryoplasma or native fresh plasma) are not always available, particularly at the regional hospitals, correctional therapy of hemostasis can be performed by administration of dry lyophilic plasma frozen in the first hours after blood collection. This plasma is injected if it is concentrated (diluted in 1/3 volume of solvent specified on the label), the bolus dose is

1,000−1,500 ml (based on plasma dose indicated on the bottle) and more. There are fibrinogen and other procoagulants, which fill the lost protein in the dry plasma. Administration of cryoprecipitate and other drugs, called procoagulants, is not necessary because of the absence of antithrombin III.

It is necessary to underline the ineffectiveness and dangers of fibrinogen prescription. Firstly, it is an unbalanced drug in the system of hemostasis (there is no sufficient quantity of another procoagulant such as antithrombin III). Secondly, administration of fibrinogen with large amount of FDPs is dangerous, because fibrinogen may be block with these products in fibrin-monomeric complexes. It leads to blockage of microcirculation.

Platelet transfusion or platelet concentrate is prescribed for profuse bleeding in acute thrombocytopenia.

The replenishment of lost blood and treatment of anemia are important. If the volume of blood loss is less than 800−1000 ml, the best thing to do is to administrate of rheopolyglucin and other blood substitutes. The replacement of RBCs is necessary in severe blood loss. Freshly prepared (immediately before transfusion) "warm" citrated blood is the drug of choice in massive blood loss. You can also transfuse erythrocyte mass or the washed fresh erythrocytes. Introduction of preserved blood during 3 days or more is not prescribed because of blood clots that enhance DIC. Reinfusion of blood from the body cavity of a patient contraindicated in DIC because its the risk of developing syndrome.

The normalization of red blood indexes is not necessary, because of promotion of DIC ("syndrome of massive transfusion, homological blood syndrome") by massive blood transfusion, caused the circulatory overload, agglutination of red blood cells.

If the levels of erythrocytes and hematocrit are higher than $2{,}5\times10^{12}$/l and 22%, respectively, the replenishment of blood is required.

It is necessary to account the amount of transfused fluid because its large volume can cause pulmonary edema. Lasix and osmotic diuretics are prescribed in this situation. The patient should receive mechanical ventilation with positive pressure in the lungs during exhalation.

Plasmapheresis is used for subacute and chronic forms of DIC, especially for inflectional and septic DIC, for toxic forms, and immunocomplex pathologies. During one procedure doctors remove 500−1000 ml of plasma, replacing it by fresh frozen plasma and blood substitute. The number of procedures is determined by the cause of disease. Dopamine is injected in acute insufficiency of kidneys (intravenously, in 0.05% solution with 5 % glucose solution at a rate of 5−10 drops per 1 min; the daily dose of dopamine is 200−400 mg). Forced diuresis, transfusion of fresh frozen plasma are also prescribed for acute insufficiency of kidneys.

Professor G. M. Glants of Lviv Institute of Hematology and Blood Transfusion has developed an original method of treatment for acute renal failure, associated with prostin E_2 (prostaglandin E) administration. Prostin E_2 is administered intravenously, slowly (2−5 mg prostin E_2 in 300 ml of isotonic solution of sodium chloride) 1 time a day. The infusion of the drug is repeated withing 3−5 days, depending on the severity of acute renal failure. Hemodialysis is prescribed in case of ineffectiveness of such treatment.

DIC prevention depends on qualified timely treatment to prevent the development of this syndrome and in rejection of unjustified transfusions of preserved blood in large volumes.

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Abbreviations

AIHA – autoimmune hemolytic anemia
ALL – acute lymphoblastic leukemia
AML – acute myeloid leukemia
ATG – antithymocyte globulin
CA – circulating anticoagulants
CBC – complete blood count
CLL – chronic lymphocytic leukemia
CML – chronic myeloid leukemia
DDAVP – 1-deamino-8-D-arginine vasopressin
DIC – disseminated intravascular coagulation
DNA – deoxyribonucleic acid
FAB – French-American-British
GI – gastrointestinal bleeding
G-6-PD – glucose 6 phosphate dehydrogenase
H – hypochromia
HA – hemolytic anemias
Hb – hemoglobin
HSP – Henoch-Schonlein purpura
HUS – hemolytic-uremic syndrome
IDA – iron deficiency anemia
ICD-10 – International Classification of Diseases, 10^{th} Rev.
ITP – idiopatic thrombocytopenic purpura
Ig – immunoglobulin
M – microcytosis
MCV – mean corpuscular volume
MCHC – mean the corpuscular hemoglobin concentration
$NSAID_s$ – nonsteroidal anti-inflammatory drugs
PA – pernicious anemias
FDP_s – fibrin degradation products
PT – prothrombin time
RBC_s/WBC_s – red/white blood cells
TTP – thrombotic thrombocytopenic purpura
vWF/vWD – von Willebrand factor/disease

Content P.

Навчальне видання

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ВНУТРІШНЯ МЕДИЦИНА: ГЕМАТОЛОГІЯ

Навчальний посібник

(Англійською мовою)

За загальною редакцією
В. Ф. Орловського, Н. В. Деміхової

Художнє оформлення обкладинки Є. В. Нікітюка
Редактор С. В. Чечоткіна
Комп'ютерне верстання О. М. Чернацької

Формат 60×84/16. Ум. друк. арк. 7,91. Обл.-вид. арк. 6,98. Тираж 300 пр. Зам. №

Видавець і виготовлювач
Сумський державний університет,
вул. Римського-Корсакова, 2, м. Суми, 40007
Свідоцтво суб'єкта видавничої справи ДК № 3062 від 17.12.2007.