Ministry of Health of Ukraine
Zaporizhzhya State Medical University

PRINCIPALS OF DIAGNOSTICS, TREATMENT AND PREVENTION OF THE DISEASES OF THE BLOOD AND BLOOD-FORMING ORGANS

Textbook for practical lessons and individual work of 4th course students by specialty "Internal Medicine"

Zaporizhzhya, 2015

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This textbook content methods of educational process organization by Module 1, Content Module 4 "Principals of diagnostics, treatment and prophylaxis of the blood disorders" according to demands of Program of Educational Discipline "Internal Medicine".
In the textbook there are methodical guidelines for practical lessons and student's individual work, clinical protocols of medical help for patients with diseases of the blood and blood-forming organs and tests for evaluation of students' initial knowledge level.

CONTENT

THEMATIC PLAN OF LECTURES FOR CONTENT MODULE 4: «Bases of diagnostics, treatment and prophylaxis of basic diseases of blood and blood-forming organs»

№	Topic	Hours
19.	Anemia	2
20.	Acute and chronic leukemia	2
TOTAL		**4**

THEMATIC PLAN OF PRACTICAL LESSONS FOR CONTENT MODULE 4: «Bases of diagnostics, treatment and prophylaxis of basic diseases of blood and blood-forming organs»

№	Topic	Hours
26	Anemia	5
27	Acute and chronic leukemia	5
28	Lymphoma and multiple myeloma	5
29	Hemophilia and thrombopenic purpura	5
TOTAL		**20**

THEMATIC PLAN OF INDIVIDUAL OUT-OF-CLASS STUDENTS WORK FOR CONTENT MODULE 4: «Bases of diagnostics, treatment and prophylaxis of basic diseases of blood and blood-forming organs»

№	Topic	Hours
1.	Preparing to practical lessons including:	
	- Acquire the skills to set emergency care in bleeding - Acquire the skills to determinate blood group - Acquire the skills to transfuse blood and components - Acquire the skills to estimate full blood count and myelogram	13
2.	Curation of patient and writing of diagnosis with it substantiation	2
3.	Individual work: • Reporting of summary on practical lesson • Report on the clinical conference of clinical bases of the department • Report of case history on practical lesson • Writing down of thesis and articles	1
TOTAL		**16**

THEME 26

ANEMIAS

Studying hours: 5 hours

I. Actuality of theme. Anemia is a global public health problem affecting both developing and developed countries with major consequences for human health as well as social and economicdevelopment. It occurs at all stages of the life cycle, but is more prevalent in pregnant women and young children. Although the primary cause is iron deficiency, it is seldom present in isolation.. More frequently it coexists with a number of other causes, such as malaria, parasitic infection, nutritional deficiencies, and hemoglobinopathies.

Anemia affects 1.62 billion people globally, corresponding to 24.8% of the world population (McLean et al, 2009). Iron deficiency is the most common cause and even in the developed world an estimated 30-40% of preschool children and pregnant women have iron depletion (WHO, 2008).

Iron deficiency anemia (IDA) is the most common nutritional disorder worldwide and accounts for approximately one-half of anemia cases. IDA is about 80% in structure anemic states. Chronic blood loss, gastrointestinal disorders, pregnancy, childbirth and lactation, infections, cancer, malabsorption (coeliac disease), poor dietary intake and NSAID use lead to the development of iron deficiency in adult. In 2002, iron deficiency anemia (IDA) was considered to be among the most important contributing factors to the global burden of disease.

Hemolytic anemia - a group of diseases that are accompanied by increased destruction of red blood cells. Significant spread of these diseases in the population, and the need differentiation jaundice that accompany these diseases, necessitating the study of this subject by students.

B12-folate-deficiency anemia is the group of anemia, which develop as a result of violation of synthesis of DNA and RNA and complicate motion and treatment of large group of diseases among which: atrophic gastritis, gastric cancer, diseases of the operated stomach, disease of intestines (including helminthic invasion, dysbacteriosis), liver diseases, hemoblastosis, pregnancy, alimentary insufficiency and others like that.

All the foregoing leads relevance of the topic and the need to study it.

II. Purposes of lesson.

- teach students to collect anamnesis of patients with details of complaints to recognize the main symptoms and syndromes in anemia;
- familiarize students with research methods that are used to diagnose anemia, indications for their use and it technique, the diagnostic value of them;
- teach students to interpret the full blood count (FBC) in various forms of anemia;
- teach students choose the right treatment regimen and support therapy for anemia.

Student must know (α1, α 2):

– Modern definition of different forms of anemia.
– Modern classification of anemia.
– Etiology, pathogenesis of the most common forms of anemia.
– The main clinical syndromes in sideropenia, hemolytic states.

Student should be able to (α 3):

- Conduct differential diagnosis: chronic iron, B12 and folate deficiency anemia, hypo- and aplastic anemia.
- Conduct treatment of deficiency, hemolytic, hypoplastic forms of anemia.
- Render the first aid in anemic coma.

Students must acquire the skills (α 3):

- History taking and physical examination of patients with various forms of anemia.
- Interpretation FBC in anemia.
- Know the features of iron metabolism and hemoglobin synthesis.
- Know the factors lead to the development of IDA, B12 (folate)-DA, aplastic and hemolytic anemia.
- Know the laboratory investigations for hemolysis.

- Know the main drugs for treatment of major types of anemia and to be able to write recipes.
- Be able to perform a hemotransfusion, transfusion of platelets and plasma.

III. Goals the development of personality (educational goals).

– The student must learn to follow the rules of conduct, principles of medical ethics and deontology bedside with anemia;
– Possess the ability to establish psychological contact with the patient and his family;
– Acquires a sense of professional responsibility for the timeliness and adequacy of quality medical care.

IV. Interdisciplinary integration.

Discipline	To know	To be able to
1	*2*	*3*
1. Previous (providing)		
Normal anatomy	The structure of human hemopoiesis, its blood supply and innervation	
Histology	Blood cells	To estimate normal blood count and at pathology
Normal physiology	Physiology of blood system, normative indices of laboratory and instrumental methods of investigation, their value	To estimate investigation data of blood system
Pathological physiology	Key links of pathogenesis of anemia	
Pathological anatomy	Morphological features of development of anemia	To analyze and interpret data of clinical inspection and investigation of patient
Pharmacology	Pharmacokinetics, pharmacodynamics, side effects of drugs used in the treatment of patients with anemia	Assign treatment, depending on age and individual characteristics of the patient, disease period. Define the optimal mode of reception and administration of drugs. Write recipes.
Propedeutics Internal Medicine	Basic stages and methods of clinical examination of the patient	Collect complaints, medical history, history of life, identify the main risk factors for anemia, conduct an objective examination of the patient's organs and systems, to identify the clinical features of anemia, interpret these additional laboratory and instrumental studies
Radiation diagnostics	Normative indices of abdominal and bones X-ray, CT-scan and US in anemia	Interpret data of X-ray and CT images, sonograms
Neurology	Neurological syndromes	Estimate neurological symptoms and take differential diagnostics with clinical manifestation of anemia
2. Followings (provided)		
Emergency states	Risk factors and clinical manifestations of urgent conditions in patients with anemia: bleeding	Render first aid in emergency conditions in patients with anemia: bleeding
Hospital therapy	Clinical manifestation of complications and atypical forms of anemia, tactic of treatment	To determine the clinical displays of complications and atypical forms of anemia, able to administer treatment
3. Interdisciplinary integration		
Renal failure	Clinical manifestations of kidney disorders	Establish the characteristic clinical signs of kidney disorders and to perform differential diagnosis of anemia
Rheumatoid arthritis	Clinical manifestations of rheumatoid arthritis	To determine the clinical signs of rheumatoid arthritis and to conduct differential diagnostics with anemia
Hepatolienal	Clinical manifestations of	Establish the characteristic clinical signs of

syndrome	hepatolienal syndrome	hepatolienal syndrome and to perform differential diagnosis of anemia
Leukemia	Clinical manifestations of acute and chronic leukemia	Establish the characteristic clinical signs of leukemia and to perform differential diagnosis of anemia
Hemorrhagic syndromes	Clinical manifestations of hemophilia, thrombocytopenia, Schönlein-Henoch disease	Establish the main clinical signs of hemorrhagic syndromes and to perform differential diagnosis of anemia

V. Table of contents of theme of lesson

The WHO defines anemia as hemoglobin below 13 g/dL in men over 15 years, below 12 g/dL in non-pregnant women over 15 years, and below 11 g/dL in pregnant women.

Classification of anemias.

There are two main classifications of anemia:

- the pathogenetic and etiological classification, based on the cause of the anemia;
- the morphological classification based on the characteristics of the red cell.

These two classifications are complimentary to each other, as the clinical investigation of a patient with anemia involves two distinct steps:

- determination of the morphological type of anemia;
- determination of the cause of the anemia.

The etiological classification of anemia can be further subdivided into either:

- hyporegenerative ;
- hyperregenerative;
- normoegenerative.

Reticulocytes are larger than mature red cells and contain portions of polyribosomal RNA material. Supravital stains of peripheral blood detect these reticulated cells, and their number permits an assessment of the marrow's response to the peripheral anemia. The reticulocyte count provides an easy means of implicating either the marrow or the periphery as the source of the anemia. This differentiation dictates the further investigative work up by narrowing the focus to the bone marrow in reticulocytopenic states but to peripheral loss/or hemolytic abnormalities when reticulocytosis is present. The normal count is as follows: adults and children - 0.2-2.0%.

N.B. Anemia + Low reticulocyte count = Hyporegenerative anemia.

Anemia + High reticulocyte count = Hyperegenerative anemia.

Morphological Classification.

An alternative classification of anemia is based on the morphology of the red cells, usually their size and staining characteristics.

Red cell indices

MCV (mean corpuscular volume).

The average volume of RBC (fl) =Hct × 10/ RBC count (m/μL) **NR= 80-96 fl.**

MCH (mean corpuscular hemoglobin).

The average content of Hb in average RBC. It is directly proportional to the amount of Hb and RBC size.

MCH =Hb/RBC count (m/μL)*10 (pg). **NR= 27-32 pg**.

MCHC (mean corpuscular hemoglobin concentration).

Express the average concentration of hemoglobin per unit volume of RBC. It defined as the ratio of the weight of hemoglobin to volume of RBC.

MCHC=Hb (g/dl)/Hct (%)× 100 (%). **NR= 32-36%.**

Red cells may be normal in size (normocytic), large (macrocytic), or small (microcytic). They stain pink with the stains used in hematology, but there is a central area of pallor which does not exceed 1/3 the diameter of the cell. Cells stained in this way are normochromic. If the central area of pallor is greater than 1/3 the diameter of the cell it is described as hypochromic.

On this basis the anemia may be classified as

1) microcytic (MCV is < 80 fl).
   - IDA.
   - Thalassemia (non thalassemic conditions associated with microcytosis).
   - Anemia chronic disorders (ACD) (rheumatoid arthritis, Hodgkin's lymphoma, chronic infection, neoplasia).
   - Sideroblastic anemia (hereditary, lead poisoning).
2) normocytic (MCV is 80-100 fl).
   - Nutritional anemia (iron deficiency, cobalamin, folate).
   - Anemia of renal insufficiency.
   - Hemolytic anemia.
   - Red cell intrinsic causes: membranopathy, enzymopathy, hemoglobinopathy.

- Red cell extrinsic causes: immune-mediated, microangiopathic, associated with infection, chemical agent (spider venoms), metabolic.
- ACD.
- Primary bone marrow disorder.
- Causes that are intrinsic to hematopoietic stem cells: bone marrow aplasia (idiopathic, PNH, Fanconi syndrome), pure red cell aplasia (acquired, congenital, Diamond-Blackfan syndrome), myelodysplastic syndrome.
- Extrinsic causes: drugs, toxins, radiation, viruses, immune-mediated, bone marrow infiltration (metastatic and lymphoma).

3) macrocytic (MCV >100 fL).

- Megaloblastic anaemia (nutritional:vitamin B12 and folate deficiency).
- Drugs (hydroxyurea, zidovudine, methotrexate).
- Drug-induced hemolytic anemia.
- Dyserythropoiesis, myelodysplastic syndrome, clonal hematologic disorder.
- Hereditary hematologic disorders.
- Excess alcohol intake, liver disease, smoking.
- Hypothyroidism, Waldenström's macroglobulinemia.
- Copper deficiency, bone marrow aplasia, erythroblastopenic anemia.
- Down syndrome.
- Chronic obstructive pulmonary disease.

PATHOLOGICAL CLASSIFICATION

1. Blood loss

- Acute.
- Chronic.

2. Decreased production

- Disturbance of proliferation and differentiation.
- Of stem cells.
- Of erythroblasts.

3. Defective Hb synthesis

- Increased destruction.
- Intracarpuscular (Intrinsic) defects.
- Extracarpuscular (Extrinsic) defects.

Classification of anemia, ICD-10.

Nutritional anemias D50-D53

- D50 Iron deficiency anemia
- D51 Vitamin B12 deficiency anemia
- D52 Folate deficiency anemia
- D53 Other nutritional anemias

Hemolytic anemias D55-D59

- D55 Anemia due to enzyme disorders
- D56 Thalassemia
- D57 Sickle-cell disorders
- D58 Other hereditary hemolytic anemias
- D59 Acquired hemolytic anemia

Aplastic and other anemias and other bone marrow failure syndromes D60-D64

- D60 Acquired pure red cell aplasia (erythroblastopenia)
- D61 Other aplastic anemias and other bone marrow failure syndromes
- D62 Acute posthemorrhagic anemia
- D63 Anemia in chronic diseases classified elsewhere
- D64 Other anemias

Iron deficiency anemia.

Iron metabolism is unusual in that it is controlled by absorption rather than excretion. Iron is only lost through blood loss or loss of cells as they slough. Men and nonmenstruating women lose about 1 mg of iron per day. Menstruating women lose from 0.6 to 2.5 percent more per day. An average 132-lb (60-kg) woman might lose an extra 10 mg of iron per menstruation cycle, but the loss could be more than 42 mg per cycle depending on how heavily she menstruates. A pregnancy takes about 700 mg of iron, and a whole blood donation of 500 cc contains 250 mg of iron. Iron absorption, which occurs mostly in the jejunum, is only 5 to 10 percent of dietary intake in persons in homeostasis. In states of overload, absorption decreases. Once absorbed from the bowel, iron is transported across the mucosal cell to the blood, where it is carried by the protein transferrin to developing red cells in the bone marrow. Iron stores comprise ferritin, a labile and readily accessible source of iron, and hemosiderin, an insoluble form found predominantly in macrophages. Absorption can increase three- to fivefold in states of depletion. Dietary iron is available in two forms: heme iron, which is found in meat; and nonheme iron, which is found in plant and dairy foods. Absorption of heme iron is minimally affected by dietary factors, whereas nonheme iron makes up the bulk of consumed iron. The bioavailability of non-heme iron requires acid digestion and varies by an order of magnitude depending on the concentration of enhancers (e.g., ascorbate, meat) and inhibitors (e.g., calcium, fiber, tea, coffee, wine) found in the diet. Iron deficiency results when iron demand by the body is not met by iron absorption from the diet. Thus, patients with IDA presenting in primary care may have inadequate dietary intake, hampered absorption, or physiologic losses in a woman of reproductive age. It also could be a sign of blood loss, known or occult. IDA is never an end diagnosis; the work-up is not complete until the reason for IDA is known.

Risk factors for iron deficiency.

Inadequate iron intake/absorption/stores

- Vegetarian eating styles, especially vegan diets
- Macrobiotic diet
- Low intakes of meat, fish, poultry or iron fortified
- foods
- Low intake of foods rich in ascorbic acid
- Frequent dieting or restricted eating
- Chronic or significant weight loss
- Meal skipping
- Substance abuse
- Recent immigrant from developing country
- Special health care needs
-

Increased iron requirements/losses

- Gastrointestinal bleeding (esophagitis, esophageal varices, hiatus hernia, peptic ulcer, inflammatory bowel disease, haemorrhoids, carcinoma: stomach, colorectal)
- Malabsorption **(**coeliac disease, atrophic gastritis)
- Heavy/lengthy menstrual periods
- Rapid growth
- Pregnancy (recent or current)
- Chronic use of aspirin or NASD (ibuprofen) or corticosteroid use
- Intensive physical training
- Frequent blood donations
- Parasitic infection

Clinical manifestations

Clinical symptoms and signs of IDA are usually nonspecific (signs of anemic syndrome), unless the anemia is severe. Fatigue is the most common symptom. Patients may complain of pallor, weakness, headache, palpitations, dizziness, dyspnea and irritability. Rarely pica develops, where there is a craving for non-food items such as ice and dirt (signs of sideropenic syndrome). IDA may also impair temperature regulation and cause pregnant women to feel colder than normal. Storage iron is depleted before a fall in Hb and as iron is an essential element in all cells, symptoms of iron deficiency may occur even without anemia: these include fatigue, irritability, poor concentration and hair loss.

Anemic syndrome

- Extreme fatigue
- Pale skin
- Weakness
- Shortness of breath
- Headache
- Dizziness or lightheadedness

- Cold hands and feet
- Irritability
- Fast heartbeat

Sideropenic syndrome (these changes are believed to be due to a reduction in the iron-containing enzymes in the epithelium and gastrointestinal tract).

- Atrophy of the skin.
- Inflammation or soreness of your tongue, angular stomatitis.
- Nail changes such as koilonychia (spoon shaped nails) result in brittle, flattened nails.
- Tinnitus, and taste disturbance. Unusual cravings for non-nutritive substances, such as ice, dirt or starch.
- An uncomfortable tingling or crawling feeling in your legs (restless legs syndrome).
- Oesophageal and pharyngeal webs: Plummer-Vinson syndrome (association of postcricoid dysphagia, upper esophageal webs, and IDA).

Investigations.

- Full clinical history and physical examination.
- Full blood count (FBC) and blood film examination.
- Hematinic assays (serum ferritin, vitamin B12, folate).
- Urea and electrolytes, liver function tests.
- Fecal occult bloods.
- Midstream urine (occult blood loss).
- Fibreoptic and/or barium studies of gastrointestinal tract.
- Pelvic ultrasound (females, if indicated).

Laboratory investigations

***Full blood count, blood film and red cell indices*.** A FBC may show low Hb, MCV, mean cell hemoglobin (MCH), and MCHC; a blood film may confirm presence of microcytic hypochromic red cells and characteristic 'pencil cells'. However, microcytic, hypochromic indices may also occur in hemoglobinopathies. In addition, for milder cases of iron deficiency, the MCV may not have fallen below the normal range. Some analyses will give a percentage of hypochromic red cells present. This is said to be a sensitive marker of functional iron deficiency, but is not available on all analyses.

Hematocrit: this is the percentage of the blood volume made up by red blood cells. Normal levels are generally between 34.9 and 44.5 percent for adult women and 38.8 to 50 percent for adult men

Serum iron: measures how much iron is circulating in the blood and is lower than normal in a person with IDA.

Total iron binding capacity (TIBC): measure the amount of transferrin in the blood that is capable of transporting iron to RBCs or body stores and is higher than normal in a person with IDA;

Transferrin saturation: measures the percentage of iron-binding sites on transferrin that are occupied by iron and is lower that normal in a person with IDA.

Serum Fe and TIBC are unreliable indicators of availability of iron to the tissues because of wide fluctuation in levels due to recent ingestion of Fe, diurnal rhythm and other factors such as infection. Transferrin saturation fluctuates due to a diurnal variation in serum iron and is affected by the nutritional status (Adams et al, 2007). This may lead to a lack of sensitivity and specificity.

Serum ferritin is a stable glycoprotein which accurately reflects iron stores in the absence of inflammatory change. It is the first laboratory test to become abnormal as iron stores decrease and it is not affected by recent iron ingestion. It is generally considered the best test to assess iron-deficiency, although it is an acute phase reactant and levels will rise when there is active infection or inflammation. **A serum ferritin concentration of <12 μg/dl is diagnostic of IDA**. However, serum ferritin may be raised above 12–15 μg/dl in patients with ID and concurrent chronic inflammation, malignancy, or hepatic disease, although if the concentration is >100 μg/dl, ID is almost certainly not present.

Zinc protoporphyrin (ZPP). ZPP increases when iron availability decreases, as zinc, rather than iron, is incorporated into the protoporphyrin ring. This gives an indication of availability of iron to the tissues. Serum ZPP has the advantage of not being influenced by the plasma dilution and levels rise in the third trimester. It is affected by inflammation and infection although less so than is the serum ferritin. Red blood

cell ZPP has greater sensitivity and specificity for iron depletion (Schifman et al, 1989) but is rarely performed.

Soluble transferrin receptor (sTfR). Measurement of sTfR is reported to be a sensitive measure of tissue iron supply and isnot an acute-phase reactant (Choi et al, 2000). The transferrin receptor is a transmembrane protein which transports iron into the cell. Circulating concentrations of sTfR are proportional to cellular expression of the membrane-associated TfR and therefore give an accurate estimate of iron deficiency. There is little change in the early stages of iron store depletion, but once iron deficiency is established, the sTfR concentration increases in direct proportion to total transferrin receptor concentration. However, this is an expensive test which restricts its general availability.

Bone marrow iron. A bone marrow sample stained for iron has been considered the gold standard for assessment of iron stores; however, this test is clearly too invasive and not practical for any but the most complicated cases, where the underlying cause or causes of anemia are not identifiable by simpler means.

Management of iron deficiency anemia

The treatment modalities for managing IDA will depend on the underlying cause. The aim of treatment should be to restore hemoglobin levels and MCV to normal and replenish body stores. If this cannot be achieved, consideration should be given to further evaluation. A trial of iron therapy is simultaneously diagnostic and therapeutic. Ferritin should be checked first if the patient is known to have a hemoglobinopathy but otherwise microcytic or normocytic anemia can be assumed to be caused by iron deficiency until proven otherwise. Assessment of response to iron is both cost and time effective. A rise in Hb should be demonstrable by 2 weeks and confirms iron deficiency. If hemoglobinopathy status is unknown, it is reasonable to start iron whilst screening is being performed. Screening should be carried out immediately, in accordance with the NHS sickle cell and thalassaemia screening programme guidelines. Although severe anemia can affect the results of hemoglobinopathy testing, with a reduction in HbA2 of up to 0.5%, there is no justification for delay (Ryan et al, 2010). An effective system of reviewing results is imperative. If there has been no improvement in Hb by two weeks, referral should be made to secondary care to consider other causes of anemia, such as folate deficiency.

Oral iron therapy. Oral iron therapy is usually adequate for most patients; it is an efficient, well tolerated and cost-effective way to replace iron stores. Historically, ferrous sulfate has been used to treat IDA because it is better absorbed by the gastrointestinal tract and causes fewer side effects (heartburn, abdominal pain, nausea, diarrhea and constipation). When complexes or chelated forms of iron are used the gastrointestinal symptoms are minimal.

Common oral iron preparations

Iron salt	Elemental iron (%)	Typical dosage (mg)	Elemental iron/dose (mg)
Ferrous sulfate	20	325, t.i.d	65
Ferrous sulfate exsiccated	30	200, t.i.d.	65
Ferrous gluconate	12	325, t.i.d.	36
Ferrous fumarate	33	325, b.i.d.	106

Oral iron replacement therapy with gradual replenishment of iron stores and restoration of haemoglobin is the preferred treatment. Oral ferrous salts are the treatment of choice (ferric salts are less well absorbed) and should take the form of ferrous sulphate 200 mg three times daily (providing 65 mgx3 = 195 mg elemental iron/day). Alternative preparations include ferrous gluconate and ferrous fumarate. Effective iron replacement therapy should result in a rise in haemoglobin concentration of around 1 g/l per day (about 20 g/l every three weeks), but this varies from patient to patient. Once the haemoglobin concentration is within the normal range, iron replacement should continue for three months to replenish the iron stores.

Response to oral iron therapy. The treatment of IDA should include a strategy for measuring response to iron therapy. Historically, a 2 g/dl improvement in Hb levels has been considered an appropriate response to iron supplementation; yet, other parameters may be more reliable. When refractory IDA is nonresponsive to oral iron therapy, H. pylori infection and chronic gastritis are often to blame. The eradication of H. pylori is warranted to maximize oral iron therapy in the recovery from IDA.

Parenteral iron therapy. Parenteral iron therapy is indicated when there is absolute non-compliance with, or intolerance to, oral iron therapy or proven malabsorption (RCOG, 2007). It circumvents the natural gastrointestinal regulatory mechanisms to deliver non-protein bound iron to the red cells. As free iron may lead to the production of hydroxyl radicals with potential toxicity to tissues, iron deficiency should be

confirmed by ferritin levels before use of parenteral preparations. Contraindications include a history of anaphylaxis or reactions to parenteral iron therapy, first trimester of pregnancy, active acute or chronic infection and chronic liver disease (Perewusnyk et al, 2002). Facilities and staff trained in management of anaphylaxis should be available.

Despite the introduction of newer intravenous (i.v.) iron preparations with improved safety profiles, practitioners seem hesitant to administer i.v. iron. Four parenteral iron preparations are available. Two are iron dextrans that differ in molecular weight and the other two preparations are iron salt preparations, ferric gluconate and iron sucrose. Iron sucrose has a higher availability for erythropoiesis than iron dextran and experience suggests a good safety profile in pregnancy (Bayoumeu et al, 2005). Its use is limited by the total dose that can be administered in one infusion, requiring multiple infusions. The newer preparations, iron III carboxymaltose and Iron III isomaltoside aim to overcome this problem, with single dose administration in an hour or less (Lyseng-Williamson et al, 2009; Gozzard,2011).

Iron III carboxymaltose (Ferrinject) is a ferric hydroxide carbohydrate complex, which allows for controlled delivery of iron within the cells of the reticuloendothelial system (primarily bone marrow) and subsequent delivery to the iron binding proteins ferritin and transferrin. It is administered intravenously, as a single dose of 1000mg over 15 minutes (maximum 15mg/kg by injection or 20 mg/kg by infusion). Randomised controlled trials have shown non-inferiority (Van Wyk et al, 2007; Breymann et al, 2007) and superiority (Seid et al, 2008) to oral ferrous sulphate in the treatment of IDA in the postpartum period, with rapid and sustained increases in Hb. Iron III isomaltoside (Monofer) is an intravenous preparation with strongly bound iron in spheroid iron-carbohydrate particles, providing slow release of bioavailable iron to iron binding proteins. There is rapid uptake by the reticuloendothelial system and little risk of release of free iron. An erythropoietic response is seen in a few days, with an increased reticulocyte count. Ferritin levels return to the normal range by 3 weeks as iron is incorporated into new erythrocytes. Doses >1000mg iron can be administered in a single infusion (Gozzard, 2011).

The preparation that may be given intramuscularly is low molecular weight iron dextran. Compared with oral iron, intramuscular iron dextran has been shown in a randomized controlled trial to reduce the proportion of women with anemia (Komolafe et al, 2003). However injections tend to be painful and there is significant risk of permanent skin staining. Its use is therefore generally discouraged (Pasriche et al, 2010, Solomons et al, 2004) but if given, the Z-track injection technique should be used to minimize risk of iron leakage into the skin. The advantage of IM iron dextran is that, following a test dose, it can be administered in primary care, although facilities for resuscitation should be available as there is a small risk of systemic reaction.

Common intravenous iron preparations

	Cosmofer Iron (III) hydroxide	***Venofer*** Iron (III) hydroxide sucrose complex	***Ferinject*** Iron(III) carboxymaltose	***Monofer*** Iron (III) isomaltoside
Dose of elemental iron	50mg/ml	20mg/ml	50mg/ml	100mg/ml
Test dose required as per manufacturer	Yes, before every intravenous dose, once before intramuscular treatment	First dose new patients only	No	No
Routes of administration total dose	Slow intravenous injection Intravenous infusion of total dose Intramuscular injection	Slow intravenous injection Intravenous infusion	Slow intravenous injection Intravenous infusion	Slow intravenous injection Intravenous infusion
Able to administer total dose	Yes (up to 20mg/kg body weight over 4-6 hours)	No	Yes (up to 20mg/kg body weight maximum of 1000mg/week over 15mins)	Yes (up to 20mg/Kg body weight
Half life	5 hours	20 hours	7-12 hours	5 hours
Dosage over	100-200mg per IV injection up to 3 times	Total IV single dose no more than	1000mg by IV injection up to	100-200mg per IV injection up to 3 times

60 mins	a week. Total dose infusion up to 20mg/kg body weight over 4-6 hours) (100mg IM into alternate buttocks daily in active patients in bed ridden up to 3 times a week)	200mg, can be repeated up to 3 times in 1 week	15mg/kg/week. Total dose infusion up to 20mg/kg body weight. Maximum weekly dose of 1000mg that can be administered over 15mins.	a week. Total dose infusion up to 20mg/Kg body weight per week. Doses up to 10mg/Kg body weight can be administered over 30mins, doses greater than 10mg/kg body weight should be administered
Adverse drug related events	5% patients may experience minimal adverse events (dose related). Risk of severe anaphylaxis <1/10 000 Risk of anaphylactoid symptoms >1/1000<1/100	0.5-1.5% of patients may experience adverse events. Risk of anaphylactoid reaction >1/10 000 <1/1000	3% of patients may experience adverse events. Risk of anaphylactoid reaction >1/1000 <1/100	More than 1% of patients may experience adverse events. Risk of anaphylaxis <1/10 000 >1/1000 to <1/100 Anaphylactoid reactions

Dietary Strategies

Dietary iron sources include meat, fish and poultry, lentils, dried beans, grain products, vegetables, dried fruit, and molasses. Sources of heme iron from hemoglobin and myoglobin found in meat, fish, and poultry are effectively absorbed by receptors in the gut, while the bioavailability of non-heme iron from plants is determined by the presence of dietary factors that enhance or inhibit its absorption**.**

Alternative treatments. Blood transfusion is not indicated unless the patient has decompensated due to a drop in haemoglobin concentration and needs a more rapid rise in haemoglobin–for example, in cases of worsening angina or severe coexisting pulmonary disease. In cases of iron deficiency with serious ongoing acute bleeding blood transfusion may be required**.**

B12 - deficiency anemia (B_{12}DA).

Vitamin B_{12} (cobalamin) deficiency is a common cause of megaloblastic anemia, a variety of neuropsychiatric symptoms, and elevated serum homocysteine levels, especially in older persons. There are a number of risk factors for vitamin B_{12} deficiency, including prolonged use of metformin and proton pump inhibitors. Vitamin B12 is a water-soluble vitamin that is crucial to normal neurologic function, red blood cell production, and DNA synthesis. Vitamin B12 is essential for three enzymatic processes: the conversion of homocysteine to methionine; the conversion of methylmalonic acid to succinic coenzyme A; and the conversion of 5-methyltetrahydrofolate to tetrahydrofolate, a process necessary for DNA synthesis and red blood cell production. It cannot be manufactured by humans and must be regularly obtained from the ingestion of animal proteins or fortified cereal products. Gastric acid liberates vitamin B12 from animal proteins, after which it combines with intrinsic factor produced by gastric parietal cells and is absorbed in the terminal ileum. Pernicious anemia, which is characterized by an autoimmune-mediated chronic atrophic gastritis, is a classically described cause of vitamin B12 deficiency; other common causes include postsurgical malabsorption, dietary deficiencies, and vitamin B12 malabsorption from food. Because of extensive hepatic stores of vitamin B12, there may be a five- to 10-year delay between the onset of deficiency and the appearance of clinical symptoms.

Risk factors for Vitamin B_{12} deficiency

- Decreased ileal absorption (Crohn disease, ileal resection, tapeworm infestation)
- Decreased intrinsic factor
- Atrophic gastritis
- Postgastrectomy syndrome (includes Roux-en-Y gastric bypass)
- Genetic (transcobalamin II deficiency)
- Inadequate intake (vegetarians)
- Alcohol abuse
- Older persons

- Prolonged medication use (histamine H2 blockers, metformin, proton pump inhibitors)

Clinical manifestations of B_{12}DA

Cutaneous

- Hyperpigmentation
- Vitiligo

Gastrointestinal

- Glossitis
- Jaundice

Hematologic

- Anemia (macrocytic, megaloblastic). *Anemic syndrome* include pallor, tachycardia, weakness, fatigue, and palpitations.
- Leucopenia
- Thrombocytopenia

Neuropsychiatric

- Cognitive impairment
- Gait abnormalities
- Irritability
- Peripheral neuropathy.

Laboratory investigations

The initial laboratory assessment of a patient with suspected vitamin B12 deficiency should include a complete blood count and a serum vitamin B12 level.

Complete blood count. Classic hematologic expression of vitamin B12 deficiency is a megaloblastic macrocytic anemia characterized by an elevated mean corpuscular volume and mean corpuscular hemoglobin, and a peripheral smear containing macroovalocytes and hypersegmented neutrophils.

The research studies and clinical laboratories define vitamin B12 deficiency at a level of less than 150 pg per mL (110.67 pmol per L), or in some cases 200 pg per mL. Vitamin B12 levels greater than 350 pg per mL seem to be protective against symptoms of vitamin B12 deficiency.

In patients with clinical symptoms of vitamin B12 deficiency and low levels of serum vitamin B12, ***no further confirmatory testing is generally needed before treatment is initiated***. Verification with serum methylmalonic acid and/or serum homocysteine level may be necessary in asymptomatic patients with high-risk conditions, symptomatic patients with low-normal levels of vitamin B12 (200 to 350 pg per mL), or symptomatic patients in whom vitamin B12 deficiency is unlikely but must be excluded. Elevated levels of serum homocysteine and methylmalonic acid have been shown to be highly sensitive markers for vitamin B12 deficiency. Testing is widely available, but expensive, and multiple conditions may falsely elevate serum homocysteine and methylmalonic acid levels. Because serum methylmalonic acid level is as sensitive as, but more specific than, serum homocysteine level for vitamin B12 deficiency, it is the confirmatory test of choice. Serum holotranscobalamin level, which is reduced in vitamin B12 deficiency, compared favorably with homocysteine and methylmalonic acid levels as a confirmatory test in one study, but further trials are needed before its widespread use for this purpose can be recommended.

Pernicious anemia should be suspected in patients without an obvious cause of malabsorption or who have a coexisting autoimmune disorder, such as vitiligo or thyroiditis. The Schilling test, which was previously used to diagnose pernicious anemia, is no longer available in the United States, and testing for elevated levels of anti-intrinsic factor antibodies and elevated serum gastrin or pepsinogen is recommended. Because of the association between pernicious anemia and a higher incidence of gastric cancer and carcinoids, it is important to pursue a diagnosis and, if confirmed, recommend endoscopy.

Treatment

Treatment of clinical vitamin B12 deficiency has traditionally been accomplished by intramuscular injection of crystalline vitamin B12 at a dosage of 1 mg weekly for eight weeks, followed by 1 mg monthly for life. In a 2005 Cochrane review, patients who received high dosages of oral vitamin B12 (1 to 2 mg daily) for 90 to 120 days had an improvement in serum vitamin B12 similar to patients who received intramuscular injections of vitamin B12. These results were consistent in patients regardless of the etiology of their vitamin B12 deficiency, including malabsorption states and pernicious anemia. Given the lower cost and ease of administration of oral vitamin B12, this might be a reasonable choice for replacement in many

patients. In cases of megaloblastic anemia, reticulocytosis generally occurs within a few days, and the hematocrit generally normalizes over several weeks. Advanced neurologic symptoms may not respond to replacement. Vitamin B12 has been demonstrated to be safe in doses up to 1,000 times the recommended dietary allowance and is safe in pregnancy. The bioavailability of sublingual vitamin B12 appears to be equivalent to oral vitamin B12, but there is no evidence that sublingual delivery offers any advantage over oral preparations.

Prevention

The Institute of Medicine recommends daily consumption of 2.4 mcg of vitamin B_{12} in adults older than 18 years to prevent vitamin B_{12} deficiency. Because crystalline formulations are better absorbed than naturally occurring vitamin B_{12}, patients older than 50 years should consume foods fortified with vitamin B_{12} and vitamin B_{12} supplements, rather than attempting to get vitamin B_{12} strictly from dietary sources. Strict vegetarians must obtain their vitamin B_{12} from supplements or consumption of fortified cereal products to prevent deficiency. Because of the high incidence of vitamin B_{12} deficiency in patients undergoing gastric bypass surgery, daily prophylactic supplementation with 1 mg is recommended.

Hemolytic Anemia

Hemolysis presents as acute or chronic anemia, reticulocytosis, or jaundice. The diagnosis is established by reticulocytosis, increased unconjugated bilirubin and lactate dehydrogenase, decreased haptoglobin, and peripheral blood smear findings. Premature destruction of erythrocytes occurs intravascularly or extravascularly. The etiologies of hemolysis often are categorized as acquired or hereditary. Common acquired causes of hemolytic anemia are autoimmunity, microangiopathy, and infection. Immune-mediated hemolysis, caused by antierythrocyte antibodies, can be secondary to malignancies, autoimmune disorders, drugs, and transfusion reactions. Microangiopathic hemolytic anemia occurs when the red cell membrane is damaged in circulation, leading to intravascular hemolysis and the appearance of schistocytes. Infectious agents such as malaria and babesiosis invade red blood cells. Disorders of red blood cell enzymes, membranes, and hemoglobin cause hereditary hemolytic anemias. Glucose-6-phosphate dehydrogenase deficiency leads to hemolysis in the presence of oxidative stress. Hereditary spherocytosis is characterized by spherocytes, a family history, and a negative direct antiglobulin test. Sickle cell anemia and thalassemia are hemoglobinopathies characterized by chronic hemolysis.

Hemolysis is the destruction or removal of red blood cells from the circulation before their normal life span of 120 days. While hemolysis can be a lifelong asymptomatic condition, it most often presents as anemia when erythrocytosis cannot match the pace of red cell destruction. Hemolysis also can manifest as jaundice, cholelithiasis, or isolated reticulocytosis.

Pathophysiology.

There are two mechanisms of hemolysis. Intravascular hemolysis is the destruction of red blood cells in the circulation with the release of cell contents into the plasma. Mechanical trauma from a damaged endothelium, complement fixation and activation on the cell surface, and infectious agents may cause direct membrane degradation and cell destruction. The more common extravascular hemolysis is the removal and destruction of red blood cells with membrane alterations by the macrophages of the spleen and liver. Circulating blood is filtered continuously through thin-walled splenic cords into the splenic sinusoids (with fenestrated basement membranes), a spongelike labyrinth of macrophages with long dendritic processes.1 A normal 8-micron red blood cell can deform itself and pass through the 3-micron openings in the splenic cords. Red blood cells with structural alterations of the membrane surface (including antibodies) are unable to traverse this network and are phagocytosed and destroyed by macrophages.

Classification of hemolytic anemias.

1. Hereditary:

- Membrane (hereditary spherocytosis, hereditary elliptocytosis, hereditary stomatocytosis (Hydrocytosis), hereditary pyropoikilocytosis, hereditary xerocytosis).
- Metabolism (glucose 6-phosphate- dehydrogenase deficiency, pyruvate kinase deficiency, glutathione reductase deficiency).
- Hemoglobinopathies (sickle cell anemia (SS), CC, SC, and S-β thalassemia).

2. Acquired:

- Immune:

- *Autoimmune* (warm antibody type, cold antibody type*).*
- *Alloimmune* (hemolytic disease of the newborn, allografts, especially stem cell transplantation, hemolytic transfusion reactions).
- *Drug associated.*

- Red cell fragmentation syndromes.
- March hemoglobinuria.
- Infections (malaria, clostridia).
- Chemical and physical agents (drugs, industrial/domestic substances, burns).
- Secondary (liver and renal disease).

- Paroxysmal nocturnal hemoglobinuria.

Anemia most often is discovered through laboratory tests, but the history and physical examination can provide important clues about the presence of hemolysis and its underlying cause. The patient may complain of dyspnea or fatigue (caused by anemia). Dark urine and, occasionally, back pain may be reported by patients with intravascular hemolysis. The skin may appear jaundiced or pale. A resting tachycardia with a flow murmur may be present if the anemia is pronounced. Lymphadenopathy or hepatosplenomegaly suggest an underlying lymphoproliferative disorder or malignancy; alternatively, an enlarged spleen may reflect hypersplenism causing hemolysis. Leg ulcers occur in some chronic hemolytic states, such as sickle cell anemia.

Hematologic tests.

Along with anemia, a characteristic laboratory feature of hemolysis is *reticulocytosis*, the normal response of the bone marrow to the peripheral loss of red blood cells. In the absence of concomitant bone marrow disease, a brisk reticulocytosis should be observed within three to five days after a decline in hemoglobin. In a minority of patients, the bone marrow is able to chronically compensate, leading to a normal and stable hemoglobin concentration. The anemia of hemolysis usually is normocytic, although a marked reticulocytosis can lead to an elevated measurement of mean corpuscular volume, because the average mean corpuscular volume of a reticulocyte is 150 fL. Review of the peripheral blood smear is a critical step in the evaluation of any anemia. Along with an assessment for pathognomonic red blood cell morphologies, such as spherocytes or schistocytes, examination of the white blood cells and platelets for coexisting hematologic or malignant disorders is essential.

Chemistry tests.

The destruction of red blood cells is characterized by increased unconjugated bilirubin, increased lactate dehydrogenase, and decreased haptoglobin levels. Lactate dehydrogenase and hemoglobin are released into the circulation when red blood cells are destroyed. Liberated hemoglobin is converted into unconjugated bilirubin in the spleen or may be bound in the plasma by haptoglobin. The hemoglobin-haptoglobin complex is cleared quickly by the liver, leading to low or undetectable haptoglobin levels

Urinary tests. In cases of severe intravascular hemolysis, the binding capacity of haptoglobin is exceeded rapidly, and free hemoglobin is filtered by the glomeruli. The renal tubule cells may absorb the hemoglobin and store the iron as hemosiderin; hemosiderinuria is detected by Prussian blue staining of sloughed tubular cells in the urinary sediment approximately one week after the onset of hemolysis. Hemoglobinuria, which causes red-brown urine, is indicated by a positive urine dipstick reaction for heme in the absence of red blood cells.

Membranopathies.

Hereditary spherocytosis is an autosomal dominant disorder caused by mutations in the red blood cell membrane skeleton protein genes. With a weakened protein backbone anchoring its lipid bilayer, the membrane undergoes a progressive deterioration in structure, resulting in a spherocyte, the characteristic abnormality seen on peripheral smear. The spherocytes are unable to pass through the splenic cords and are degraded and ingested by the monocyte-macrophage system. Although there is marked variability in phenotype, hereditary spherocytosis is typically a chronically compensated, mild to moderate hemolytic anemia. The diagnosis is based on the combination of spherocytosis noted on peripheral smear, a family history (in 75 percent of cases), and a negative DAT. The mean corpuscular hemoglobin concentration frequently is elevated. Splenectomy effectively arrests the extravascular hemolysis and prevents its long-term complications, such as cholelithiasis and aplastic crises. Because of the inherent risk of infections and sepsis, however, splenectomy generally is reserved for use in patients older than five years with moderate to

severe disease, characterized by hemoglobin concentrations of less than 11 g per dL (110 g per L) and jaundice. Partial splenectomy has been demonstrated to be effective in decreasing hemolysis while maintaining the phagocytic function of the spleen.

Hemoglobinopathies.

The thalassemias are a heterogeneous group of inherited multifactorial anemias characterized by defects in the synthesis of the alpha or beta subunit of the hemoglobin tetramer (α2, β2). The deficiency in one globin chain leads to an overall decrease in hemoglobin and the intracellular precipitation of the excess chain, which damages the membrane and leads to clinically evident hemolysis in the severe forms of alpha thalassemia (hemoglobin H disease) and beta thalassemia (intermedia and major). Beta thalassemia can be diagnosed by hemoglobin electrophoresis, which shows elevated levels of hemoglobins A2 and F, while diagnosis of alpha thalassemia requires genetic studies. Thalassemias are characterized by hypochromia and microcytosis; target cells frequently are seen on the peripheral smear.

Sickle cell anemia is an inherited disorder caused by a point mutation leading to a substitution of valine for glutamic acid in the sixth position of the β chain of hemoglobin. Membrane abnormalities from sickling and oxidative damage caused by hemoglobin S, along with impaired deformability of sickle cells, leads to splenic trapping and removal of cells. Some degree of intravascular hemolysis occurs as well. Hemoglobin electrophoresis reveals a predominance of hemoglobin S. Sickle cells are observed on the peripheral smear.

Hemolytic Anemias

Type	***Etiology***	***Associations***	***Diagnosis***	***Treatment***
Acquired				
Immune-mediated	Antibodies to red blood cell surface antigens	Idiopathic, malignancy, drugs, autoimmune disorders, infections, transfusions	Spherocytes and positive DAT	Treatment of underlying disorder; removal of offending drug; steroids, splenectomy, IV gamma globulin, plasmapheresis, cytotoxic agents, or danazol (Danocrine); avoidance of cold
Microangiopathic	Mechanical disruption of red blood cell in circulation	TTP, HUS, DIC, pre-eclampsia, eclampsia, malignant hypertension, prosthetic valves	Schistocytes	Treatment of underlying disorder
Infection	Malaria, babesiosis, Clostridium infections		Cultures, thick and thin blood smears, serologies	Antibiotics
Hereditary				
Enzymopathies	G6PD deficiency	Infections, drugs, ingestion of fava beans	Low G6PD activity measurement	Withdrawal of offending drug, treatment of infection
Membranopathies	Hereditary spherocytosis		Spherocytes, family history, negative DAT	Splenectomy in some moderate and most severe cases
Hemoglobinopathies	Thalassemia and sickle cell disease		Hemoglobin electrophoresis,	Folate, transfusions

			genetic studies	

Aplastic anemia

Aplastic anemia (AA) is a rare but heterogeneous disorder. The majority (70–80%) of these cases are categorised as idiopathic because their primary etiology is unknown. In a subset of cases, a drug or infection can be identified that precipitates the bone marrow failure/aplastic anemia, although it is not clear why only some individuals are susceptible. In approximately 15–20% of patients the disease is constitutional/inherited, where the disease is familial and/or presents with one or more other somatic abnormalities.

Aplastic anemia is defined as pancytopenia with a hypocellular bone marrow in the absence of an abnormal infiltrate and with no increase in reticulin.

Investigations required for diagnosis.

1. FBC and reticulocyte count.
2. Blood film examination.
3. HbF% in children.
4. Bone marrow aspirate and trephine biopsy, including cytogenetics.
5. Peripheral blood chromosomal breakage analysis to exclude Fanconi anaemia if <50 years.
6. Flow cytometry for GPI-anchored proteins (see note below concerning Ham test).
7. Urine haemosiderin if Ham test positive or GPI-anchored protein deficiency.
8. Vitamin B12 and folate level.
9. Liver function tests.
10. Viral studies: Hepatits A, B and C, EBV, HIV.
11. Anti-nuclear antibody and anti-dsDNA.
12. Chest X-ray.
13. Abdominal ultrasound scan and ECG.
14. Peripheral blood gene mutation analysis for dyskeratosis congenital DKC1, TERC, TERT) if clinical features or lack of response to immunosuppressive therapy.

The ***full blood count*** typically shows pancytopenia although usually the lymphocyte count is preserved. In most cases the hemoglobin level, neutrophil and platelet counts are all uniformly depressed, but in the early stages isolated cytopenia, particularly thrombocytopenia, may occur. Anemia is accompanied by reticulocytopenia, and macrocytosis is commonly noted. Careful examination of the blood film is essential to exclude the presence of dysplastic neutrophils and abnormal platelets, blasts and other abnormal cells, such as hairy cells (as seen in hairy cell leukemia). The monocyte count may be depressed but the absence of monocytes should alert the clinician to a possible diagnosis of hairy cell leukemia. In aplastic anemia, anisopoikilocytosis is common and neutrophils may show toxic granulation. Platelets are reduced in number and mostly of small size. Fetal hemoglobin should be measured pre-transfusion in children as this is an important prognostic factor in paediatric myelodysplastic syndrome (MDS) which may feature in the differential diagnosis of pancytopenia in children**.**

Both a bone marrow aspirate and trephine biopsy are required. Bone marrow aspiration and biopsy may be performed in patients with severe thrombocytopenia without platelet support, providing that adequate surface pressure is applied. Fragments are usually readily obtained from the aspirate. Difficulty obtaining fragments should raise the suspicion of a diagnosis other than aplastic anemia. The fragments and trails are hypocellular with prominent fat spaces and variable amounts of residual hemopoietic cells. Erythropoiesis is reduced or absent, dyserythropoiesis is very common and often marked, so this alone should not be used to make a diagnosis of MDS. Megakaryocytes and granulocytic cells are reduced or absent; dysplastic megakaryocytes and granulocytic cells are not seen in aplastic anemia. Lymphocytes, macrophages, plasma cells and mast cells appear prominent. In the early stages of the disease, one may also see prominent haemophagocytosis by macrophages, as well as background eosinophilic staining representing interstitial oedema. A trephine is crucial to assess overall cellularity, to assess the morphology of residual hemopoietic cells and to exclude an abnormal infiltrate. In most cases the trephine is hypocellular throughout but sometimes it is patchy, with hypocellular and cellular areas. Thus, a good quality trephine of at least 2 cm is essential. A ‘hot spot’ in a patchy area may explain why sometimes the aspirate is normocellular. Care should be taken to avoid tangential biopsies as subcortical marrow is normally ‘hypocellular’. Focal hyperplasia of erythroid or granulocytic cells at a similar stage of maturation may be

observed. Sometimes lymphoid aggregates occur, particularly in the acute phase of the disease or when the aplastic anaemia is associated with systemic autoimmune disease, such as rheumatoid arthritis or systemic lupus erythematosus. The reticulin is not increased and no abnormal cells are seen. Increased blasts are not seen in aplastic anaemia, and their presence either indicates a hypocellular MDS or evolution to leukemia.

To define aplastic anemia there must be at least two of the following hemoglobin <100 g/l, platelet count <50*10^9/l, neutrophil count <1.5*10^9/l.

Differential diagnosis of pancytopenia and a hypocellular bone marrow.

The above investigations should exclude causes of a hypocellular bone marrow with pancytopenia other than aplastic anemia. These include:

Hypocellular MDS/acute myeloid leukemia (AML) can sometimes be difficult to distinguish from aplastic anemia. The following features of MDS are not found in aplastic anemia: dysplastic cells of the granulocytic and megakaryocytic lineages, blasts in the blood or marrow.

Hypocellular acute lymphoblastic leukemia (ALL) occurs in 1–2% of cases of childhood ALL. Overt ALL usually develops within 3–9 months of the apparent bone marrow failure. In contrast to aplastic anemia, the neutropenia is usually more pronounced than the thrombocytopenia and sometimes there is an increase in reticulin within the hypocellular bone marrow. Immunophenotyping may help confirm the diagnosis. Treatment should not be deferred in severe aplastic anemia in children just in case they turn out to have ALL.

Hairy cell leukaemia classically presents with pancytopenia but the accompanying monocytopenia is a constant feature of this disorder. It is usually difficult or impossible to aspirate on bone marrow fragments. In addition to the typical interstitial infiltrate of hairy cells with their characteristic ‘fried egg’ appearance in the bone marrow trephine, there is always increased reticulin.

Lymphomas, either Hodgkin lymphoma or non-Hodgkin lymphoma and myelofibrosis may sometimes present with pancytopenia and a hypocellular bone marrow. The bone marrow biopsy should be examined very carefully for foci of lymphoma cells or fibrosis which may be seen in only a small part of the trephine. Since lymphocytes are often prominent in aplastic anemia, immunophenotyping should be performed. Myelofibrosis is usually accompanied by splenomegaly and the absence of an enlarged spleen in the presence of marrow fibrosis should alert one to secondary malignancy. Marker studies and gene rearrangement studies will help to confirm the diagnosis of lymphoma.

Supportive care

Transfusional support. Support with red cell and platelet transfusions is essential for patients with aplastic anemia to maintain a safe blood count. It is recommended to give prophylactic platelet transfusions when the platelet count is <10*10^9/l (or <20*10^9/l in the presence of fever), rather than giving platelets only in response to bleeding manifestations.

Prevention of infection. The risk of infection is determined by the patient’s neutrophil and monocyte counts. Patients with aplastic anemia are at risk of bacterial and fungal infections. Aplastic anemia patients who are severely neutropenic (<0.5*10^9/l) should ideally be nursed in isolation when in hospital and should receive prophylactic antibiotics and antifungals, regular mouth care including an antiseptic mouthwash, such as chlorhexidine, and food of low bacterial content. Prophylactic antibiotics are given to help prevent Gram-negative sepsis, either a combination of two non-absorbable antibiotics, such as neomycin and colistin, or a quinolone antibiotic, such as ciprofloxacin. Patients with aplastic anemia are at high risk of fungal infection, including Aspergillus. The drugs of choice are itraconazole and posaconazole, the latter of which has not yet been shown to be superior in efficacy to itraconazole.

Allogeneic bone marrow transplantation (BMT) from an HLA-identical sibling donor is the initial treatment of choice for newly diagnosed patients with aplastic anemia if they have severe or very severe aplastic anemia, are younger than 40 years (although there is controversy concerning the upper age limit for BMT) and have an HLA compatible sibling donor.

Immunosuppressive therapy is recommended for patients with non-severe aplastic anemia who are transfusion-dependent patients with severe or very severe disease who are >40 years old and younger patients with severe or very severe disease who do not have an HLA-identical sibling donor.

VI. Plan and organizational structure of lesson – See Appendix 1.

VII. Materials for control and methodical providing lesson.

VII.1 control materials for a preparatory stage lesson.

Questions to control the output level of knowledge skills and abilities:

1. Formulate a definition of anemia.
2. Identify the etiology of anemia.
3. Specify the key pathogenesis of anemia.
4. Name the modern clinical classification of anemia.
5. Name the typical clinical manifestations of anemia.
6. Make a plan for laboratory and instrumental examination of patients with anemia.
7. Indicate complications of anemia.
9. Name the principles of treatment of anemia.
10. Indicate the main groups of drugs used in the treatment of anemia.
11. Prophylaxis of anemia.

Tests of II level:

1. (On a substitution, α=2). Basic factor leads to IDA is_____.

Standard of answer: chronic hemorrhage.

2. (On a sequence, α =2). Set the faithful sequence of suction of iron in an organism:

1) Transferrin carries iron in plasma.
2) Hemoglobin breakdown of senescent RBCs.
3) Intracellular transport of iron.
4) Iron stored as either ferritin or hemosiderin.

Standard of answer: 2), 1), 4), 3).

3. (With a plural choice, α=2). What promotes suction of iron most of all?

1) Organic acids, especially ascorbic acid
2) Cellulose contained in sifting
3) Animal albumen
4) Albumen, phosphates, high maintenance of fat
5) Simple carbohydrates (lactose, fructose, sorbitol).
6) Poliphenol (tea, coffee).

Standard of answer: 1), 3), 5).

4. (On accordance, α=2) Define accordance the groups of preparations to drugs used for treatment in patients with IDA.

1) Ferrum-gluconate
2) Ferrum-sulfate
3) Combined drugs (iron+ascorbinic acid)
4) Preparation of iron for parenteral use

A) Actiferrin
B) Feronal
C) Ferum-lek
D) Sorbifer-durules

Standard of answer: 1 -B; 2 - A; 3-D; 4 -C;

Tasks of II level:

1. What laboratory index does allow take diagnosis of autoimmune hemolytic anemia?
   A. Saccharose's test
   B. *Coombs' test
   C. Autohaemolytic test
   D. Determination of osmotic RBC resistance
   E. Bleeding time
2. What anemia is characteristic for decrease serum iron level?
   A. Hypoplastic
   B. Megaloblastic
   C. Minkowsky-Shauffard
   D. *Iron deficiency
   E. Thalassemia
3. What signs are characteristic the sideropenic syndrome?
   A. Glossitis
   B. Angular stomatitis
   C. Koilonychia
   D. *All listed
   E. Esophagitis
4. Patient of 39, complaints of periodic dizziness, enhanced fatigue. Objectively: skin and visible mucus pale. Ps - 100 per min. BP is 85/45 mm hg. Cor - tones are rhythmic, sinus tachycardia. Blood count: RBC - 2,2 *10^12/L, Hb - 90 g/L, serum iron level - 7 mcmol/l, total binding iron capacity - 42,6 mcmol/L. What drugs does it follow to begin treatment from?
   A. *Iron drugs orally
   B. Iron drugs i/v, i/m
   C. Aminicapronic acid, dicinon, vikasol
   D. Transfusion of erythromass
   E. Transfusion of fresh-frozen plasma
5. The patient, 50 years old, complains of a general weakness, dizziness, heaviness in the upper half of abdomen, paresthesia of finger-tips upper and lower extremities. Objectively: a skin is icteric, tongue of raspberry color, smooth and shiny, Hepatomegaly. Blood count: Hb - 90 g/L, RBC - 2,3 tera/L, retic. - 0,2%, CI -1,2, macrocytosis; Zholli bodies, Kebot rings. What is tactic of treatment?
   A. *Vitamin B12 i/m
   B. Desferal i/m
   C. Blood transfusion
   D. Iron drugs orally
   E. Prednisolone orally
6. Patient of 24, was directed on consultation to the hematologist concerning a repeated icterus, splenomegaly. Blood test: RBC - $3.1*10^{12}$/l, Hb - 108 g/L, CI - 1.0, reticul. - 15%, diameter of RBC- 5.0 mcm. Total bilirubin - 65 mcmol/l, undirect - 60 mcmol/l, direct - 5.0 mcmol/l. Sterkobilin level increased in faeces, urine. Your initial diagnosis:
   A. *Hereditary spherocytosis
   B. Gilbert's disease
   C. Addison-Biermer anemia
   D. Thalassemia
   E. Marchiafava-Micheli disease
7. What anemia is an enhanced contain in blood of fetal hemoglobin at?
   A. Microspherocytosis
   B. B12-folate-deficiency anemia
   C. Aplastic anemia
   D. *Thalassemia
   E. Autoimmune hemolytic anemia

VII.2 Materials of the methodical providing of the basic stage of lesson

Professional algorithm of curation of patient

(reference card) for forming of practical skills and abilities

№	Task	Sequence execution	Notes, warnings on self-control
1	*2*	*3*	*4*
1	To conduct the objective inspection of patient with anemia	1. To conduct collection of complaints, anamnesis of disease. 2. Carefully to collect anamnesis of life of patient. 3. To conduct a review patient. 4. To investigate the cardiovascular system of the patient (palpation, percussion).	Pay attention to the features, characteristics and conditions of anemic, sideropenic syndrome. Set risk factors and comorbidities lead to anemia. Estimate the general state the patient, position in bed, color and moisture of the skin and mucous membranes, the presence of swelling of veins of neck, edema on extremities. Pay attention to the rhythm of the pulse, presence pulse deficit, its tension and size on both hands, apical, its properties, limits of absolute and relative cardiac dullness, their changes in heart rate (tachy- or bradycardia, extrasystoles), BP (increase then decrease SBP)
		5. Conduct heart auscultation and great vessels. 6. Conduct auscultation of the lungs. 7. To investigate the digestive system.	Pay attention to the incresed I tone, systolic murmurs. Set the presence of dyspnea, rales. Identify pain zones, hepatosplenomegaly.
2	To formulate a previous diagnosis.	1. Formulate and preliminary diagnosis. 2. Substantiate all components of previous diagnosis on the basis of complaints, medical history and life, physical examination	Based on the current classification of anemia formulate a preliminary diagnosis and substantiate every component.
3	To estimate the indexes of additional laboratory researches.	1. To estimate blood count. 2. To interpret indices of iron, B12, folate metabolism. 3. To estimate myelogram.	To pay attention in the presence of anemia, micro-macrocitosis, pancytopenia, reticulocytosis. To interpret iron level, ferritin, TIBC, B12, folate level.
4	To interpret information of additional instrumental researches.	1. To interpret FGDS, colonoscopy, abdominal sonogram.	To pay attention on pathology leads to bleeding, hepatosplenomegaly, lymphadenopathy.
5.	To conduct differential diagnostics.	1. Consistently find similarities in the complaints, medical history of the disease and life, objective status, data, laboratory and instrumental methods of examination of the patient and with similar nosology. 2. Find the differences between the complaints, according to medical history and life, objective symptoms, results of laboratory and instrumental methods of research and patient with similar	Particular attention should be paid to the differential diagnosis of leukemia, renal failure, cancer, lymphomas, hemophilia, thrombocytopenia

		nosology. 3. Based on the identified differences exclude similar disease from the list of possible diagnoses. 4. To the differential diagnosis by the aforementioned algorithm with all nosology that have similar clinical signs with the patient. 5. Given the impossibility to exclude anemia from a list of possible diagnoses draw a conclusion the greatest likelihood of such a diagnosis.	
6.	To formulate a final clinical diagnosis.	1. Formulate a final clinical diagnosis. 2. Based on the diagnosis, analysis of additional laboratory and instrumental methods conducted differential diagnosis to justify all the elements of the final clinical diagnosis.	Based on the current classification of anemia formulate previous diagnosis indicating the stage and severity of exacerbations, complications of the underlying disease and concomitant diseases.
7.	To administer treatment a patient.	1. Life style recommendations. 2. To administer drugs, other methods of treatment.	To indicate the regime and diet. Considering the age, the severity of disease, presence of complications and concomitant pathology appoint modern medical treatment according to the anemia guidelines.

VII.3 Materials of control for the final stage of lesson

Tests of III level (α=3).

Task №1

Female, 37 years. Complaints about a weakness, fatigue, dizziness, poor appetite, difficulty at a meal swallowing, desire to eat a chalk. Anamnesis: during pregnancy 5 years ago she had hemoglobin 86 g/l and used iron drugs. Objective: skin and visible mucosa are pale. Breathing is normal. Pulse 96/min. Tones of heart loud, soft systolic murmur above an apex. BP 100/70 mm hg. Angular stomatitis, brittle, flattened nails. Menstruations are regular for 5 days, with the severe loss of blood. Blood count: RBC.-3,4.*10^{12}/l, Hb-72 g/l, Reticul.-2%, ESR-7 mm/h. Mycrocytosis.

1) What is your diagnosis?
2) What methods need for verification of diagnosis?
3) What tactic of treatment?

Standard of answer:

1) Iron deficiency anemia, moderate.
2) Blood count, upper and lower GI fibroscopy or barium meal test, indices of iron metabolism (ferritin, TIBC, iron level).
3) Oral iron drugs (ranferon, sorbifer, actiferrin) 100 mg t.i.d. to the 3th months. Prevention: oral iron drugs 30-70 mg/day during 7-10 days according menstrual cycle.

VIII. Materials of the methodical providing of self-study of students: a reference card is for organization of independent work of students with educational literature

Task	Instructions
To learn etiology of anemias	List the basic etiologic factors of anemias
To learn pathogenesis of anemias	To select the key links of pathogenesis of anemias
To learn the clinical manifestation of	To set symptoms and clinical syndromes which enable to

anemias	offer the previous diagnosis of anemias
To learn the diagnostic criteria of anemias	To make the structural scheme of disease
To learn the investigation (laboratory, instrumental)	To make a plan of examination of patient with anemia
To learn specific changes of images and analyses at anemias	List the basic diagnostic criteria of anemias according to data of investigations
To conduct differential diagnostics, set a final clinical diagnosis	Substitute the basic components of diagnosis in accordance with modern classification, and to conduct a differential diagnosis
To administer the individual treatment patient with anemia	Wright down the list of prescriptions include the regime, diet, drug therapy considering the age, the severity of disease, presence of complications and concomitant pathology

THEME 27

ACUTE AND CHRONIC LEUKEMIA.

Studying time: 5 hours.

I. Actuality of theme. Leukemia, lymphoma, myeloma and myelodysplastic syndromes are types of cancer that can affect the bone marrow, the blood cells, the lymph nodes and other parts of the lymphatic system. These cancers are all related since each are likely a result from acquired changes to the DNA of a single stem cell.

An estimated 48,610 new cases of leukemia are expected to be diagnosed in the US in 2013. Cases of chronic leukemia account for 4.5 percent more cases than acute leukemia. Most cases of leukemia occur in older adults; the median age at diagnosis is 66 years. The most common types of leukemia in adults are AML and CLL. The most common type of leukemia in children and adolescents younger than 20 years is ALL. Most cases of CML occur in adults. In 2010, the latest year for which data are available, about 3.3 percent of new cases of leukemia in children and adolescents younger than 20 years are CML. Almost 2 percent of all cases of CML are in adolescents ages 15 to 19 years. Between 1975 and 2010, the incidence of AML hasremained consistent overall. Incidence rates for all types of leukemia are higher among males than among females. In 2013, males are expected to account for approximately 57 percent of the new cases of leukemia.

Leukemia strikes males and females of all ages. The cause of most cases of leukemia is not known. Extraordinary doses of radiation and certain cancer therapies are possible causes. Repeated exposure to the chemical benzene may cause AML. Automobile exhaust and industrial emissions account for about 20 percent of the total national benzene exposure. About half of US benzene exposure results from tobacco smoking or from exposure to tobacco smoke. The average smoker is exposed to about 10 times the daily intake of benzene compared to nonsmokers.

The goal of treatment for leukemia is to bring about a complete remission. Complete remission means that there is no evidence of disease and the individual returns to good health with normal blood and marrow cells. Relapsed leukemia indicates return of the cancer cells and the return of disease signs and symptoms. For acute leukemia, a complete remission that lasts five years after diagnosis often indicates long-term survival. Treatment centers report increasing numbers of people with leukemia who are in complete remission at least five years after diagnosis of their disease.

II. Purposes of lesson.

Student to become familiar with (α1):

- the place of leukemia (LE) in the structure of hemoblastosis, prevalence in different age groups;
- the statistics on morbidity, incidence of complications, mortality, immediate and remote prognosis patients with LE;
- the history of scientific study of LE.

Student must know (α2):

– etiology of LE;
– clinical classification of LE.
– manifestations of leukemia;
– laboratory and instrumental diagnostic of LE
– complications of LE;
– principles of treatment of LE.

Students must acquire the skills (α 3):

– History taking and physical examination of patients with LE, to reveal main symptoms and syndromes.
– To detect etiological and pathogenetic factors.
– To detect clinical manifestations of LE.
– To detect complications of LE.
– To take and substantiate initial diagnosis.
– To substantiate administration invasive and noninvasive investigations, indications and contraindications.
– To plan laboratory and instrumental investigations of patient (according to guidelines of LE).

To capture practical skills (α 3):

- To interpret laboratory and instrumental data.
- To take differential diagnosis, substantiate and formulate clinical diagnosis of LE.
- To recommend diet, lifestyle modifications in consideration of stage, severity of disease and concomitant diseases.
- To prescribe treatment, disease-prevention service in consideration of stage, severity of disease and concomitant diseases.

III. Goals the development of personality (educational goals).

- The student must learn to follow the rules of conduct, principles of medical ethics and deontology bedside with LE;
- Possess the ability to establish psychological contact with the patient and his family;
- Acquires a sense of professional responsibility for the timeliness and adequacy of quality medical care.

IV. Interdisciplinary integration.

Discipline	To know	To be able to
1	*2*	*3*
1. Previous (providing)		
Normal anatomy	The structure of human hemopoiesis, its blood supply and innervation	
Histology	Blood cells	To estimate normal blood count and at pathology
Normal physiology	Physiology of blood system, normative indices of laboratory and instrumental methods of investigation, their value	To estimate investigation data of blood system
Pathological physiology	Key links of pathogenesis of LE	
Pathological anatomy	Morphological features of development of LE	To analyze and interpret data of clinical inspection and investigation of patient
Pharmacology	Pharmacokinetics, pharmacodynamics, side effects of drugs used in the treatment of patients with LE	Assign treatment, depending on age and individual characteristics of the patient, disease period. Define the optimal mode of reception and administration of drugs. Write recipes.
Propedeutics Internal Medicine	Basic stages and methods of clinical examination of the patient	Collect complaints, medical history, history of life, identify the main risk factors for LE, conduct an objective examination of the patient's organs and systems, to identify the clinical features of anemia, interpret these additional laboratory and instrumental studies
Radiation diagnostics	Normative indices of abdominal and bones X-ray, CT-scan and US in LE	Interpret data of X-ray and CT images, sonograms
Neurology	Neurological syndromes	Estimate neurological symptoms and take differential diagnostics with clinical manifestation of LE
2. Followings (provided)		
Emergency states	Risk factors and clinical manifestations of urgent conditions in patients with LE: bleeding	Render first aid in emergency conditions in patients with LE: bleeding
Hospital therapy	Clinical manifestation of complications and atypical forms of LE, tactic of treatment	To determine the clinical displays of complications and atypical forms of LE, able to administer treatment
3. Interdisciplinary integration		
Lymphomas	Clinical manifestations of lymphomas	Establish the characteristic clinical signs of lymphomas and to perform differential diagnosis of LE
Leukemoid reactions	Clinical manifestations of leukemoid	To determine the clinical signs and

	reactions	possible reasons of leukemoid reactions and to conduct differential diagnostics with leukemia
Hepatolienal syndrome	Clinical manifestations of hepatolienal syndrome	Establish the characteristic clinical signs of hepatolienal syndrome and to perform differential diagnosis of anemia
Aplastic anemia	Clinical manifestations of anemia	Establish the characteristic clinical signs of aplastic anemia and to perform differential diagnosis of LE
Hemorrhagic syndromes	Clinical manifestations of hemophilia, thrombocytopenia, Schönlein-Henoch disease	Establish the main clinical signs of hemorrhagic syndromes and to perform differential diagnosis of LE

V. Table of contents of theme of lesson

"Leukemia" is the term used to describe the four major types of leukemia: Acute Lymphoblastic Leukemia (ALL), Acute Myeloid Leukemia (AML), Chronic Lymphocytic Leukemia (CLL) and Chronic Myeloid Leukemia (CML). The terms "myeloid" or "myelogenous" and "lymphoid," "lymphocytic" or "lymphoblastic" denote the cell types involved. In general, leukemia is characterized by the uncontrolled accumulation of blood cells. However, the natural history of each type, and the therapies used to treat people with each type, are different.

Signs of acute leukemia may include easy bruising or bleeding (because of platelet deficiency), paleness or easy fatigue (because of anemia), recurrent minor infections or poor healing of minor cuts (because of an inadequate white cell count). These signs are not unique to leukemia and may be caused by other, more common conditions. Nonetheless, they do warrant medical evaluation. The diagnosis of leukemia requires specific blood tests, including an examination of cells in the blood and marrow. People who have chronic leukemia may not have major symptoms; they may be diagnosed as a result of a periodic physical examination and testing.

Classification of leukemia, ICD-10.

Lymphoid leukemia *C91- >*

- C91.*0 Acute lymphoblastic leukemia* (ALL)
- C91.00 ALL not having achieved remission
- C91.01 ALL in remission
- C91.02 ALL in relapse
- C91.1 *Chronic lymphocytic leukemia of B-cell type*
- C91.10…… not having achieved remission
- C91.11…… in remission
- C91.12…… in relapse
- C91.3 *Prolymphocytic leukemia of B-cell type*
- C91.30…… not having achieved remission
- C91.31…… in remission
- C91.32…… in relapse
- C91.4 *Hairy cell leukemia*
- C91.40…… not having achieved remission
- C91.41…… in remission
- C91.42…… in relapse
- C91.5 *Adult T-cell lymphoma/leukemia (HTLV-1-associated)*
- C91.50…… not having achieved remission
- C91.51…… in remission
- C91.52…… in relapse
- C91.6 *Prolymphocytic leukemia of T-cell type*
- C91.60…… not having achieved remission
- C91.61…… in remission
- C91.62…… in relapse
- C91.A *Mature B-cell leukemia Burkitt-type*
- C91.A0…… not having achieved remission

- C91.A1…… in remission
- C91.A2…… in relapse
- C91.Z *Other lymphoid leukemia*
- C91.Z0…… not having achieved remission
- C91.Z1…… in remission
- C91.Z2…… in relapse
- C91.9 *Lymphoid leukemia, unspecified*
- C91.90…… not having achieved remission
- C91.91…… in remission
- C91.92…… in relapse

C92 Myeloid leukemia

- C92.0 *Acute myeloblastic leukemia*
- C92.00…… not having achieved remission
- C92.01…… in remission
- C92.02…… in relapse
- C92.1 *Chronic myeloid leukemia, BCR/ABL-positive*
- C92.10…… not having achieved remission
- C92.11…… in remission
- C92.12…… in relapse
- C92.2 *Atypical chronic myeloid leukemia, BCR/ABL-negative*
- C92.20…… not having achieved remission
- C92.21…… in remission
- C92.22…… in relapse
- C92.3 *Myeloid sarcoma*
- C92.30…… not having achieved remission
- C92.31…… in remission
- C92.32…… in relapse
- C92.4 *Acute promyelocytic leukemia*
- C92.40…… not having achieved remission
- C92.41…… in remission
- C92.42…… in relapse
- C92.5 *Acute myelomonocytic leukemia*
- C92.50…… not having achieved remission
- C92.51…… in remission
- C92.52…… in relapse
- C92.6 *Acute myeloid leukemia with 11q23-abnormality*
- C92.60…… not having achieved remission
- C92.61…… in remission
- C92.62…… in relapse
- C92.A *Acute myeloid leukemia with multilineage dysplasia*
- C92.A0…… not having achieved remission
- C92.A1…… in remission
- C92.A2…… in relapse
- C92.Z *Other myeloid leukemia*
- C92.Z0…… not having achieved remission
- C92.Z1…… in remission
- C92.Z2…… in relapse
- C92.9 *Myeloid leukemia, unspecified*
- C92.90…… not having achieved remission
- C92.91…… in remission
- C92.92…… in relapse

ACUTE MYELOGENOUS LEUKEMIA (AML)

In adults, AML represents about 90% of all acute leukemias. The incidence rises with age, occurring rarely before age 40 (<1 in 100,000), and increasing to an incidence of 16 cases per 100,000 by age 75. The

median age at diagnosis is 65 years. The etiology of AML is still largely unknown. Genetic, drug, environmental, and occupational factors have been identified as potentially leukemogenic, but most patients present with de novo AML. Risk factors associated with the development of AML include benzene exposure, ionizing radiation, and prior exposure to cytotoxic chemotherapy (particularly alkylating agents used for treatment of cancer, connective tissue disease, or immune disorders). Individuals with constitutional genetic defects, such as Down's syndrome and Klinefelter's syndrome, have an increased incidence of AML. Other genetic disorders associated with chromosomal instability and increased chromosome breakage, such as Fanconi's anemia, Bloom's syndrome, ataxia telangiectasia, and germline TP53 mutations, are also associated with increased incidence of AML. AML may result from transformed preleukemic cells, such as those found in myelodysplastic syndromes (MDS). The MDS are a group of clonal, stem cell disorders characterized by refractory cytopenias, dysplastic changes in the bone marrow, and a likelihood of transformation to acute leukemia.

AML is believed to be caused by the malignant transformation of a single hematopoietic stem cell. Leukemic cells are characterized by clonal proliferation and/or a block in normal differentiation and maturation. Clonal hematopoiesis persists in about 30% of patients who achieve clinical remission following treatment. The pathogenesis of AML is a multi-step process, with an initial transformation event in a hematopoietic stem cell followed in clonal descendant cells by additional genetic abnormalities. Leukemic transformation may occur at an early stage of hematopoiesis with the pluripotent stem cell, or, less often, with a committed stem cell. Differentiation commitment and the degree of maturation are seen in the leukemic phenotype. Phenotypic variants have distinctive clinical and cytogenetic associations. The pathogenesis of acute leukemia also includes a critical role for oncogenes and anti-oncogenes. About 20% to 30% of leukemia cases are associated with mutations of the RAS oncogene, the most commonly detected molecular abnormalities in AML. Control of the proliferation and differentiation of many types of cells involves RAS gene products. In summary, leukemogenesis appears to be a multistep process involving a susceptible hematopoietic cell, a genetic event (oncogenes, chromosomal translocations), and possibly environmental influences (chemical, radiation).

Classification

The WHO classification defines AML as >20% blasts in the marrow or blood. The WHO classification divides AML into 5 subtypes:

1. AML with recurrent genetic abnormalities
2. AML with multilineage dysplasia
3. AML and myelodysplastic syndromes, therapy related
4. AML not otherwise categorized
5. Acute leukemia of ambiguous lineage

The FAB Classification System for AML

Subtype	Description
M0	Acute Myeloid Leukemia Without Differentiation or Maturation
M1	Acute Myeloid Leukemia Without Maturation
M2	Acute Myeloid Leukemia With Maturation
M3	Acute Promyelocytic Leukemia (APL)
M4	Acute Myelomonocytic Leukemia
M5	Acute Monocytic Leukemia
M6	Erythroleukemia
M7	Acute Megakaryoblastic Leukemia

Clinical Presentation

Common presenting symptoms are:

- weakness, dyspnea on exertion, and fatigue reflecting anemia;
- easy bruising, gum or nose bleeding, excessive bleeding following minor injuries or dental/surgical procedures, secondary to thrombocytopenia or coagulopathy. There may also be hypertrophy of the gums (rarely);
- fever and frequent infections, particularly skin and pulmonary infections, secondary to neutropenia or leukopenia;
- Gingival hyperplasia, lymphadenopathy, hepatosplenomegaly, and skin infiltration (leukemia cutis) may be observed, which are more common in the monocytic subtypes of AML (FAB M4& M5);

- malaise and anorexia, usually without weight loss.

Up to 20% of patients present with marked elevation of WBC counts (usually exceeding 100 $x10^9$/L). These patients may develop a ***hyperleukocytosis syndrome*** requiring prompt treatment. Clinical manifestations from leukocyte microthrombi include:

- dizziness;
- stupor;
- dyspnea;
- priapism;
- pulmonary insufficiency;
- intracerebral and pulmonary;
- hemorrhage.

About 5% of all leukemic patients will have asymptomatic central nervous system (CNS) involvement (based on results from cerebrospinal fluid cytology). The risk of CNS involvement in AML is highest in patients with high circulating blast counts, elevated lactate dehydrogenase (LDH) activity, and the monocytic variants of AML.

Exams and tests

A *complete blood count* and differential is essential for diagnosis:

- blast forms;
- total WBC is elevated (most of patients), normal range or below the normal range. Markedly elevated WBC, >100x10^9/L (5-20% of patients);
- anemia and/or thrombocytopenia (most of patients).

Biochemical tests. Hyperuricemia is the most common biochemical abnormality during treatment of acute leukemia. It generally results from the high turnover rate of the proliferating leukemic cells and can lead to urate precipitation, obstructive uropathy, and acute renal failure. Tumour lysis syndrome may occur with initiation of treatment as a complication of intensive cytotoxic chemotherapy or in patients with rapidly rising or very high blast counts. This may result in potentially life-threatening metabolic complications, including hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia.

Disseminated intravascular coagulation (DIC) is common at presentation for leukemic patients, with subtype FAB M3 (acute promyelocytic leukemia). Coagulation screening is performed at initiation of workup. A positive DIC screen would typically have a prolongation of the INR and partial thromboplastin times, elevated D-dimer and decreased fibrinogen levels.

Bone Marrow Findings

Aspiration and biopsy of bone marrow, usually from the superior posterior iliac spine, is routinely performed by the hematologist to confirm the diagnosis of acute leukemia. Aspirate samples are sent for morphologic, histocytochemical, immunophenotypic, cytogenetic, and molecular analysis to enable classification of the leukemia.

Human lymphocyte antigen (HLA) typing should be done in all newly diagnosed AML patients. The typing is usually done at the time of initial diagnostic workup. This information is useful should HLA matched platelets be needed at some point in patient care, or to assist in pursuing an HLA-matched donor if an allogeneic marrow transplant is considered for subsequent management.

Treatment

The goals of therapy for AML are to eliminate the leukemic clone, and to restore normal hematopoiesis. These goals are usually achieved with ***myelosuppressive chemotherapy*** and, if successful, the result is a period of bone marrow aplasia followed by recovery of normal, polyclonal hematopoiesis. A complete remission (CR) is defined as the presence of less than 5% blasts in the bone marrow and restoration of normal blood counts. Median survival is about 2 years (for patients < 60 years) and less for older patients. Approximately 25% to 40% of patients with AML treated with chemotherapy are alive and free of disease 5 years after diagnosis.

Conventional Induction Therapy. The standard induction regimen for newly diagnosed AML consists of cytarabine (cytosine arabinoside, ara-C) plus an anthracycline, such as idarubicin (or daunorubicin). Continuous infusion of cytarabine at 200 mg/m2/day for 7 days is used with an intermittent infusion of idarubicin at 12 mg/m2/day for the first 3 days. This regimen of "7 + 3" is used at the QEII HSC, as the standard induction regimen.

Second-line Induction Therapy for Refractory disease. Second-line induction therapy may use high dose cytarabine (HDAC) or Mitoxantrone- Etoposide (NOVE) chemotherapy. If this induction fails, a third line induction is sometimes considered. The likelihood of a successful CR is lower with second and third line attempt. NOVE are generally used for second-line induction therapy. Another approach is based on the observation of a steep dose-response curve for cytarabine. Increasing doses of cytarabine, given in doses of 1 to 3 g/m2, have been used in an attempt to overcome cytarabine resistance in leukemic blasts and improve remission rates and survival.

Consolidation Chemotherapy. Patients usually receive 2 cycles of consolidation chemotherapy with either IDAC, NOVE, or less often with HDAC.

Allogeneic Stem Cell Transplantation. Allogeneic bone marrow transplantation (allo-BMT) may improve disease-free survival for patients with AML in remission.Allo-BMT may be offered to patients <55 years old with related donors who have a compatible HLA tissue type. If there is no related donor available, and if the patient is < 50 years old, stem cells from a matched-unrelated donor (MUD) may be considered (if a suitable donor is available). Autologous bone marrow transplant is less commonly offered to patients with AML in remission, but maybe considered.

Management of special situations. Hyperleukocytosis with leukostasis and, for example, pulmonary infiltrates or retinal and cerebral hemorrhages requires immediate medical treatment. Leukapheresis is an option for theinitial management of hyperleukocytosis; however, no impact on long-term outcome has been shown. In general, the recommended therapy to lower WBC is hydroxyurea, given at dosages up to 50 to 60 mg/kg per day, until WBCs are less than $10\text{-}20*10^9$/L. Until the WBC has been reduced, excessive red blood cell transfusions can lead to increased blood viscosity. Special attention should be given to the prevention of tumor lysis syndrome (eg, hydration, control of uric acid production using allopurinol or rasburicase, control of urine pH).

In patients with CNS involvement, 40 to 50 mg of cytarabine should be administered intrathecally, 2 to 3 times per week until clearance of blasts, followed by 3 further injections with the same dosage. Alternatively, liposomal cytarabine (50 mg every other week) may be given for approximately 6 cycles. For prevention of arachnoiditis, dexamethasone (4 mg three times a day [tid] p.o.) may be considered on the days of intrathecal application. Prolonged application of intrathecal therapy does not appear to be justified, given that such therapy carries the risk of complications (eg, leukencephalopathy). In patients with a CNS recurrence, craniospinal irradiation with or without intrathecal chemotherapy has also been shown to be effective; however, its impact on long-term outcome is unknown.

Supportive care

Prophylactic anti-infectious treatment. For prophylaxis and treatment of infectious diseases, prevailing institutional infectious organisms and their drug-resistance pattern should primarily be considered. Personal hygiene, dental care, and vigorous hand washing (the latter also for family and caregivers) are very important for prevention of infections. Reasonable precautions should be undertaken to protect patients from bacteria or fungi in their environment. Although eating fresh fruits and/or vegetables is often discouraged, there is little evidence that adherence to such a "neutropenic diet" prevents infections.

Invasive fungal infections are a major cause of morbidity and mortality in patients with prolonged neutropenia. Prophylaxis with itraconazole, posaconazole, or amphotericin, that is, drugs with antimold activity, reduced the risk of documented aspergillus infection and likely had some effect on mortality. A recent trial found that patients randomized to posaconazole had fewer invasive fungal infections than patients randomized to either fluconazole or itraconazole according to institutional practice.

Antibiotic prophylaxis. Bacterial infections are an important cause of morbidity and mortality in neutropenic patients after chemotherapy for AML. Antibiotic prophylaxis significantly decreased the risk of death and the risk of infection-related death. The most significant reduction in risk for all-cause mortality was observed in trials testing prophylaxis with ***quinolones***, despite the occurrence of adverse effects and development of resistance.

Growth factors. The general use of growth factors in AML cannot be recommended. However, in individual cases (eg, severe infection before expected neutrophil recovery), growth factor (either GM-CSF or G-CSF) use can be considered.

Transfusion support. The introduction of platelet transfusions has dramatically reduced mortality from hemorrhage in AML. For many years, platelet transfusions were given to keep platelet counts above $20*10^9$/L. To prevent alloimmunization, removal of contaminating leukocytes is advised. Nevertheless,

alloimmunization remains a major obstacle to effective transfusion due to antibodies to HLA class I antigens in many women with prior pregnancies or patients with prior transfusions. The antifibrinolytic agent tranexamic acid can be useful in reducing bleeding and platelet transfusion.
Red blood cell transfusion. Although evidence is lacking, it is generally accepted to keep the hemoglobin level above 8 g/dL, especially in thrombocytopenic patients.
Granulocyte transfusion. No good evidence exists to recommend granulocyte transfusions in the treatment of AML. A multicenter randomized trial to address the utility of such transfusions in the setting of infections is being conducted in the US.

ACUTE LYMPHOBLASTIC LEUKAEMIA (ALL)

ALL comprises neoplastic precursor cells committed to the B or T cell lineages. B-lineage ALL is more frequent, accounting for 85% of childhood ALL and 75% of adult ALL. ALL is primarily a disease of childhood, with 75% of cases occurring under six years of age. Cytogenetic abnormalities are seen in the leukaemic clone in the majority of cases of B-ALL and often define specific entities with unique haematological and prognostic features.
ALL is a malignant (clonal) disease of the bone marrow in which early lymphoid precursors proliferate and replace the normal hematopoietic cells of the marrow. ALL may be distinguished from other malignant lymphoid disorders by the immunophenotype of the cells, which is similar to B- or T-precursor cells. Immunochemistry, cytochemistry, and cytogenetic markers may also aid in categorizing the malignant lymphoid clone.
The malignant cells of acute lymphoblastic leukemia (ALL) are lymphoid precursor cells (ie, lymphoblasts) that are arrested in an early stage of development. This arrest is caused by an abnormal expression of genes, often as a result of chromosomal translocations. The lymphoblasts replace the normal marrow elements, resulting in a marked decrease in the production of normal blood cells. Consequently, anemia, thrombocytopenia, and neutropenia occur to varying degrees. The lymphoblasts also proliferate in organs other than the marrow, particularly the liver, spleen, and lymph nodes.

Clinical Presentation

Patients with acute lymphoblastic leukemia (ALL) present with either symptoms relating to direct infiltration of the marrow or other organs by leukemic cells or symptoms relating to the decreased production of normal marrow elements.

Fever is one of the most common symptoms of ALL, and patients with ALL often have fever without any other evidence of infection. However, in these patients, one must assume that all fevers are from infections until proven otherwise, because a failure to treat infections promptly and aggressively can be fatal. Infections are still the most common cause of death in patients undergoing treatment for ALL.

Patients with ALL often have decreased neutrophil counts, regardless of whether their total WBC count is low, normal, or elevated. As a result, these individuals are at an increased risk of infection. The prevalence and severity of infections are inversely correlated with the absolute neutrophil count (ANC). *Infections* are common when the absolute neutrophil count is less than 500/µL, and they are especially severe when it is less than 100/µL.

Symptoms of anemia are common and include fatigue, dizziness, palpitations, and dyspnea upon even mild exertion. Other patients present with signs of bleeding. *Bleeding* can be the result of thrombocytopenia due to marrow replacement. Additionally, approximately 10% of patients with ALL have disseminated intravascular coagulation (DIC) at the time of diagnosis. These patients may present with hemorrhagic or thrombotic complications. Some patients present with palpable lymphadenopathy. Others, particularly those with T-cell ALL, present with symptoms related to a large mediastinal mass, such as *shortness of breath*. Infiltration of the marrow by massive numbers of leukemic cells frequently manifests as *bone pain*. This pain can be severe and is often atypical in distribution. About 10-20% of ALL patients may present with left upper quadrant fullness and early satiety due to *splenomegaly*.

Although patients may present with symptoms of leukostasis (eg, respiratory distress, altered mental status) because of the presence of large numbers of lymphoblasts in the peripheral circulation, leukostasis is much less common in people with ALL than those with acute myelogenous leukemia (AML), and it occurs only in patients with the highest WBC counts (ie, several hundred thousand per µL). Patients with a high tumor burden, particularly those with severe hyperuricemia, can present in renal failure.

Exams and Tests

A complete blood count:

- WBC count (high, normal, or low);
- decreased absolute neutrophil count (the number of mature neutrophils plus bands per unit of volume)
- blast forms;
- anemia;
- thrombocytopenia.

Coagulation studies and chemistry profiles. Abnormalities in the prothrombin time (PT)/activated partial thromboplastin time (aPTT)/fibrinogen/fibrin degradation products may suggest concomitant disseminated intravascular coagulation (DIC), which results in an elevated PT, decreased fibrinogen levels, and the presence of fibrin split products. Schistocytes are sometimes seen if DIC is present. Most patients with ALL have an elevated lactic dehydrogenase level (LDH), and they frequently have an elevated uric acid level. In addition, liver function tests and blood urea nitrogen (BUN)/creatinine determinations are necessary before the initiation of therapy.

Bone Marrow Aspiration. Aspiration slides should be stained for morphology with either Wright or Giemsa stain. The diagnosis of ALL is made when at least 30% lymphoblasts (FAB classification) or 20% lymphoblasts (WHO classification) are present in the bone marrow and/or peripheral blood. In addition, slides should be stained with myeloperoxidase (or Sudan black) and terminal deoxynucleotidyl transferase, unless another method is used, such as flow cytometry.

Treatment

Only 20-30% of adults with ALL are cured with standard chemotherapy regimens. Consequently, all patients must be evaluated for entry into well-designed clinical trials. If a clinical trial is not available, the patient can be treated with standard therapy. Traditionally, the 4 components of ALL treatment are induction, consolidation, maintenance, and CNS prophylaxis.

Standard induction therapy typically involves either a 4-drug regimen of vincristine, prednisone, anthracycline, and cyclophosphamide or L -asparaginase or a 5-drug regimen of vincristine, prednisone, anthracycline, cyclophosphamide, and L -asparaginase given over the course of 4-6 weeks. Using this approach, CR are obtained in 65-85% of patients. The rapidity with which a patient's disease enters CR is correlated with treatment outcome. The use of consolidation chemotherapy in ALL is supported by several studies. Fiere et al. compared consolidation therapy with daunorubicin and cytosine arabinoside (Ara-C) versus no consolidation therapy in adults with ALL, demonstrating a 38% 3-year, leukemia-free survival rate for subjects receiving consolidation and maintenance therapy compared with 0% for those receiving maintenance therapy without consolidation. In a study reported by Hoelzer et al, subjects whose disease was in remission after induction received consolidation therapy consisting of dexamethasone, vincristine, and doxorubicin, followed by cyclophosphamide, Ara-C, and 6-thioguanine beginning at week 20. Subjects also received maintenance therapy with 6-mercaptopurine and methotrexate during weeks 10-20 and 28-130. The median remission of 20 months was among the longest reported at the time. The most studies have showed a benefit to consolidation therapy, regimens using a standard 4- to 5-drug induction usually include consolidation therapy with Ara-C in combination with an anthracycline or epipodophyllotoxin. With the addition of third-generation cephalosporins and sophisticated blood-banking techniques, the ability to support patients through a pancytopenic phase has increased dramatically. Two notable examples are the Memorial ALL-2 protocol and the hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) protocol.

ALL-2 protocol.

The ALL-2 protocol uses an intensive, high-dose, mitoxantrone-based, AML-style induction regimen. In a phase 1 study of high-dose mitoxantrone combined with high-dose cytosine arabinoside (Ara-C).

Hyper-CVAD regimen.

The hyper-CVAD regimen is based on the success achieved with short-term, dose-intensive chemotherapy regimens in children. It incorporates hyperfractionated cyclophosphamide and intensive doses of Ara-C and methotrexate in combination with dexamethasone and vincristine. Maintenance therapy with prednisone, vincristine (Oncovin), methotrexate, and mercaptopurine (Purinethol) is given to patients with nonmature B-cell ALL.

Supportive care

Patients with ALL as with AML have a deficiency in the ability to produce normal blood cells, and they need *replacement therapy*. Packed red blood cells are given to patients with a hemoglobin level of less than 7-8 g/dL or at a higher level if the patient has significant cardiovascular or respiratory compromise. Platelets

are transfused if the count is less than 10,000-20,000/μL. Patients with pulmonary or gastrointestinal hemorrhage receive platelet transfusions to maintain a value greater than 50,000/μL. Patients with central nervous system CNS hemorrhage are transfused to achieve a platelet count of 100,000/μL. Fresh frozen plasma is given to patients with a significantly prolonged prothrombin time (PT), and cryoprecipitate is given if the fibrinogen level is less than 100 g/d.

Antibiotics are given to all febrile patients. At a minimum, include a third-generation cephalosporin (or equivalent), usually with an aminoglycoside. Patients with persistent fever after 3-5 days of antibacterial antibiotics should have an antifungal antibiotic (liposomal or lipid complex amphotericin, new generation azole or echinocandin) added to their regimen. Patients with sinopulmonary complaints would receive anti-Aspergillus treatment. Particular care is warranted for patients receiving steroids as part of their treatment, because the signs and symptoms of infection may be subtle or even absent. The use of prophylactic antibiotics in neutropenic patients who are not febrile is controversial. However, most clinicians prescribe them for patients undergoing induction therapy. A commonly used regimen includes the following: Ciprofloxacin (PO 500 mg bid), Fluconazole (200 mg PO daily), itraconazole (200 mg PO bid), or posaconazole (200 mg PO tid), Acyclovir (200 mg PO 5 times/d) or valacyclovir (500 mg PO daily).

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

CLL is the most common leukemia in the Western world with an incidence of 4.2/100 000/year. The incidence increases to >30/100 000/year at an age of >80 years. The median age at diagnosis is 72 years. About 10% of CLL patients are reported to be younger than 55 years.

The WHO classification of hematopoietic neoplasias describes CLL as leukemic, lymphocytic lymphoma, being only distinguishable from small lymphocytic lymphoma (SLL) by its leukemic appearance. In the WHO classification, CLL is always a disease of neoplastic B cells, whereas the entity formerly described as T-CLL is now called T-cell prolymphocytic leukemia. It is important to verify that the patient has CLL and not some other lymphoproliferative disease that can masquerade as CLL, such as hairy cell leukemia, or leukemic manifestations of mantle cell lymphoma, marginal zone lymphoma, splenic marginal zone lymphoma with circulating villous lymphocytes, or follicular lymphoma. To achieve this, it is essential to evaluate the blood count, blood smear, and the immune phenotype of the circulating lymphoid cells.

The cells of origin in most patients with CLL are clonal B cells arrested in the B-cell differentiation pathway, intermediate between pre-B cells and mature B cells. Morphologically, in the peripheral blood, these cells resemble mature lymphocytes. CLL B-lymphocytes typically show B-cell surface antigens, as demonstrated by CD19, CD20dim, CD21, and CD23 monoclonal antibodies. In addition, they express CD5, which is more typically found on T cells. Because normal CD5+ B cells are present in the mantle zone of lymphoid follicles, B-cell CLL is most likely a malignancy of a mantle zone–based subpopulation of anergic self-reactive cells devoted to the production of polyreactive natural autoantibodies. CLL B-lymphocytes express extremely low levels of surface membrane immunoglobulin, most often immunoglobulin M (IgM) or IgM/IgD and IgD. Additionally, they also express extremely low levels of a single immunoglobulin light chain (kappa or lambda). An abnormal karyotype is observed in the majority of patients with CLL. The most common abnormality is deletion of 13q, which occurs in more than 50% of patients. Individuals showing 13q14 abnormalities have a relatively benign disease that usually manifests as stable or slowly progressive isolated lymphocytosis. The presence of trisomy 12, which is observed in 15% of CLL patients, is associated with atypical morphology and progressive disease. Deletion in the short arm of chromosome 17 has been associated with rapid progression, short remission, and decreased overall survival. 17p13 deletions are associated with loss of function of the tumor suppressor gene p53. Deletions of bands 11q22-q23, observed in 19% of patients, are associated with extensive lymph node involvement, aggressive disease, and shorter survival. More sensitive techniques have demonstrated abnormalities of chromosome 12. Forty to 50% of patients demonstrate no chromosomal abnormalities on conventional cytogenetic studies. However, 80% of patients will have abnormalities detectable by fluorescence in situ hybridization. Approximately 2-5% of patients with CLL exhibit a T-cell phenotype.

Clinical Presentation

Patients with CLL present with a wide range of symptoms and signs. Onset is insidious, and it is not unusual for CLL to be discovered incidentally after a blood cell count is performed for another reason; 25-50% of patients will be asymptomatic at time of presentation. Enlarged lymph nodes are the most common

presenting symptom, seen in 87% of patients symptomatic at time of diagnosis. A predisposition to repeated infections such as pneumonia, herpes simplex labialis, and herpes zoster may be noted. Early satiety and/or abdominal discomfort may be related to an enlarged spleen. Mucocutaneous bleeding and/or petechiae may be due to thrombocytopenia. Tiredness and fatigue may be present secondary to anemia; 10% of patients with CLL will present with an autoimmune hemolytic anemia. Richter syndrome or Richter transformation refers to the transformation of CLL into an aggressive large B-cell lymphoma and is seen in approximately 3-10% of cases. Patients will often present with symptoms of weight loss, fevers, night sweats, muscle wasting, (ie, B symptoms) and increasing hepatosplenomegaly and lymphadenopathy.

Exams and Tests

A complete blood count:

- absolute lymphocytosis;
- Gumprecht nuclear shadows**;**
- anemia (Hb level less110 g/L);
- thrombocytopenia (platelet count less $100*10^9$/L).

The leukemia cells found in the blood smear are characteristically small, mature lymphocytes with a narrow border of cytoplasm and a dense nucleus lacking discernible nucleoli and having partially aggregated chromatin. These cells may be found admixed with larger or atypical cells, cleaved cells, or prolymphocytes, which may comprise up to 55% of the blood lymphocytes. Finding prolymphocytes in excess of this percentage would favor a diagnosis of prolymphocytic leukemia (B-cell PLL). Gumprecht nuclear shadows, or smudge cells, found as cell debris, are other characteristic morphologic features found in CLL.

Peripheral blood flow cytometry: the presence of at least **$5*10^9$ B lymphocytes/L (5000/µL) in the peripheral blood**.

Bone marrow examination. In CLL, characteristically more than 30% of the nucleated cells in the aspirate are lymphoid. Although the type of marrow infiltration (diffuse vs nondiffuse) reflects the tumor burden and provides some prognostic information, recent results suggest that the prognostic value of BM biopsy may now be superseded by new prognostic markers. A marrow aspirate and biopsy generally are not required for the diagnosis of CLL. However, a marrow biopsy and aspirate can help evaluate for factors that might contribute to cytopenias (anemia, thrombocytopenia) that may or may not be directly related to leukemia-cell infiltration of the marrow. Because such factors could influence the susceptibility to drug-induced cytopenias, a marrow biopsy is recommended before initiating therapy. It is recommended to repeat a marrow biopsy in patients with persisting cytopenia after treatment to uncover disease- versus therapy related causes.

Treatment

Patients with early-stage CLL are not treated with chemotherapy until they become symptomatic or display evidence of rapid progression of disease. Early initiation of chemotherapy has failed to show benefit in CLL and may even increase mortality. When chemotherapy is initiated, the nucleoside analogue fludarabine is the most commonly used first-line therapy in CLL. Combination regimens have shown improved response rates in several clinical trials and include the following:

- Fludarabine, cyclophosphamide, and rituximab (FCR);
- Pentostatin, cyclophosphamide, and rituximab (PCR);
- Fludarabine, cyclophosphamide, and mitoxantrone (FCM);
- Cyclophosphamide, vincristine, and prednisone (CVP);
- Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP).

CHRONIC MYELOID LEUKEMIA (CML)

The incidence of CML ranges between 10 and 15 cases/106/year (age adjusted) without any major geographic or ethnic differences. The median age at diagnosis ranges between 60 and 65 years in Europe, but is considerably lower in countries where the population is younger. The prevalence of CML is steadily rising due to the very substantial prolongation of survival that has been achieved with targeted therapy.

CML is a myeloproliferative disorder characterized by increased proliferation of the granulocytic cell line without the loss of their capacity to differentiate. Consequently, the peripheral blood cell profile shows an increased number of granulocytes and their immature precursors, including occasional blast cells.

CML is one of the few cancers known to be caused by a single, specific genetic mutation. ***More than 90% of cases result from a cytogenetic aberration known as the Philadelphia chromosome***.

CML progresses through 3 phases: chronic, accelerated, and blast. In the chronic phase of disease, mature cells proliferate; in the accelerated phase, additional cytogenetic abnormalities occur; in the blast phase, immature cells rapidly proliferate. Approximately 85% of patients are diagnosed in the chronic phase and then progress to the accelerated and blast phases after 3-5 years. The diagnosis of CML is based on the histopathologic findings in the peripheral blood and the Philadelphia chromosome in bone marrow cells. CML is an acquired abnormality that involves the hematopoietic stem cell. It is characterized by a cytogenetic aberration consisting of a reciprocal translocation between the long arms of chromosomes 22 and 9. The translocation results in a shortened chromosome 22, an observation first described by Nowell and Hungerford and subsequently termed the Philadelphia (Ph1) chromosome after the city of discovery. This translocation relocates an oncogene called ABL from the long arm of chromosome 9 to a specific breakpoint cluster region (BCR) in the long arm of chromosome 22. The ABL oncogene encodes a tyrosine protein kinase. The resulting BCR/ABL fusion gene encodes a chimeric protein with strong tyrosine kinase activity. The expression of this protein leads to the development of the CML phenotype, through processes that are not yet fully understood. The presence of BCR/ABL rearrangement is the hallmark of CML, although this rearrangement has also been described in other diseases. It is considered diagnostic when present in a patient with clinical manifestations of CML. The initiating factor of CML is still unknown, but exposure to ionizing radiation has been implicated, as observed in the increased prevalence among of the atomic bombing of Hiroshima and Nagasaki. Other agents, such as benzene, are possible causes.

Clinical Presentation

The clinical manifestations of CML are insidious. The disease is often discovered incidentally in the chronic phase, when an elevated WBC count is revealed by a routine blood count or when an enlarged spleen is found on a general physical examination. Nonspecific symptoms of fatigue and weight loss may occur long after the onset of the disease. Loss of energy and decreased exercise tolerance may occur during the chronic phase after several months. Patients often have symptoms related to enlargement of the spleen, liver, or both. The large spleen may encroach on the stomach and cause early satiety and decreased food intake. Left upper quadrant abdominal pain described as "gripping" may occur from spleen infarction. The enlarged spleen may also be associated with a hypermetabolic state, fever, weight loss, and chronic fatigue. The enlarged liver may contribute to the patient's weight loss. Some patients with CML have low-grade fever and excessive sweating related to hypermetabolism. In some patients who present in the accelerated, or acute, leukemia phase of the disease (skipping the chronic phase), bleeding, petechiae, and ecchymoses may be the prominent symptoms. In these situations, fever is usually associated with infections. Bone pain and fever, as well as an increase in bone marrow fibrosis, are harbingers of the blast phase.

Splenomegaly is the most common physical finding in patients with chronic myelogenous leukemia (CML). In more than 50% of the patients with CML, the spleen extends more than 5 cm below the left costal margin at time of discovery. The size of the spleen correlates with the peripheral blood granulocyte counts, with the largest spleens being observed in patients with high WBC counts. A very large spleen is usually a harbinger of the transformation into an acute blast crisis form of the disease. Hepatomegaly also occurs, although less commonly than splenomegaly. Hepatomegaly is usually part of the extramedullary hematopoiesis occurring in the spleen. The blast crisis is marked by an increase in the bone marrow or peripheral blood blast count or by the development of soft-tissue or skin leukemic infiltrates. Typical symptoms are due to increasing anemia, thrombocytopenia, basophilia, a rapidly enlarging spleen, and failure of the usual medications to control leukocytosis and splenomegaly.

Exams and Tests

A complete blood count:

- leukocytosis (total WBC count of 20,000-60,000 cells/μL);
- basophilia;
- eosinophilia;
- immature granulocytes, mainly metamyelocytes, myelocytes and promyelocytes, and few or occasional myeloblasts;
- normal lymphocyte counts (low percentage due to dilution in the differential count)
- anemia (mild or moderate, normochromic and normocytic);
- platelet counts can be low, normal, or even increased in some patients (>1 million in some).

The transitional or accelerated phase of CML is characterized by poor control of blood counts with myelosuppressive medication, the appearance of peripheral blast cells (≥15%), promyelocytes (≥30%), basophils (≥20%), and reduction in platelet counts to less than 100,000 cells/µL unrelated to therapy.

Signs of transformation or accelerated phase in patients with CML are poor control of blood counts with myelosuppression or interferon, increasing blast cells in peripheral blood with basophilia and thrombocytopenia not related to therapy, new cytogenetic abnormalities, and increasing splenomegaly and myelofibrosis. In approximately two thirds of cases, the blasts are myeloid. However, in the remaining one third of patients, the blasts exhibit a lymphoid phenotype, further evidence of the stem cell nature of the original disease. Additional chromosomal abnormalities are usually found at the time of blast crisis, including additional Ph1 chromosomes or other translocations. The new technique of fluorescence in situ hybridization uses labeled probes that are hybridized to either metaphase chromosomes or interphase nuclei, and the hybridized probe is detected with fluorochromes. This technique is a rapid and sensitive means of detecting recurring numerical and structural abnormalities. Additional chromosomal abnormalities, such as an additional or double Ph1-positive chromosome or trisomy 8, 9, 19, or 21; isochromosome 17; or deletion of the Y chromosome, have been described as the patient enters a transitional form or accelerated phase of the blast crisis as the Ph chromosome persists.

Other laboratory abnormalities include hyperuricemia, which is a reflection of high bone marrow cellular turnover, and markedly elevated serum vitamin B-12–binding protein (TC-I). The latter is synthesized by the granulocytes and reflects the degree of leukocytosis.

Bone marrow examination. It is characteristically hypercellular, with expansion of the myeloid cell line (eg, neutrophils, eosinophils, basophils) and its progenitor cells. Megakaryocytes (see the image below) are prominent and may be increased. Mild fibrosis is often seen in the reticulin stain. Cytogenetic studies of the bone marrow cells, and even peripheral blood, should reveal the typical Ph1 chromosome, which is a reciprocal translocation of chromosomal material between chromosomes 9 and 22. This is the hallmark of CML, found in almost all patients with the disease and present throughout the entire clinical course of CML. In addition, the chimeric BCR/ABL messenger RNA (mRNA) that characterizes CML can be detected by polymerase chain reaction (PCR). This is a sensitive test that requires just a few cells and is useful in monitoring minimal residual disease to determine the effectiveness of therapy. BCR-ABL mRNA transcripts can also be measured in peripheral blood.

Karyotypic analysis of bone marrow cells requires the presence of a dividing cell without loss of viability because the material requires that the cells go into mitosis to obtain individual chromosomes for identification after banding. This is a slow, labor-intensive process

Treatment

The goals of treatment of chronic myelogenous leukemia (CML) are threefold and have changed markedly in the past 10 years. They are as follows:

- Hematologic remission (normal complete blood cell count and physical examination (ie, no organomegaly)).
- Cytogenetic remission (normal chromosome returns with 0% Ph-positive cells).
- Molecular remission (negative polymerase chain reaction result for the mutational BCR/ABL mRNA), which represents an attempt for cure and prolongation of patient survival.

Typically, CML has 3 clinical phases: an initial chronic phase, during which the disease process is easily controlled; then a transitional and unstable course (accelerated phase); and, finally, a more aggressive course (blast crisis), which is usually fatal. In all 3 phases, supportive therapy with transfusions of red blood cells or platelets may be used to relieve symptoms and improve quality of life.

The standard treatment of choice is now imatinib mesylate (Gleevec), which is a specific small-molecule inhibitor of BCR/ABL in all phases of CML. The chronic phase varies in duration, depending on the maintenance therapy used: it usually lasts 2-3 years with hydroxyurea (Hydrea) or busulfan therapy, but it may last for longer than 9.5 years in patients who respond well to interferon-alfa therapy. Furthermore, the advent of imatinib mesylate has dramatically improved the duration of hematologic and, indeed, cytogenetic remissions. Some patients with CML progress to a transitional or accelerated phase, which may last for several months. The survival of patients diagnosed in this phase is 1-1.5 years. This phase is characterized by poor control of the blood counts with myelosuppressive medication and the appearance of peripheral blast cells (≥15%), promyelocytes (≥30%), basophils (≥20%), and platelet counts less than 100,000 cells/µL unrelated to therapy.

VI. Plan and organizational structure of lesson – see Appendix 1

VII. Materials for control and methodical providing lesson.

VII.1 control materials for a preparatory stage lesson.

Questions to control the output level of knowledge skills and abilities:

1. Formulate a definition of LE.
2. Identify the etiology of LE.
3. Specify the key concepts in pathogenesis of LE.
4. Name the modern clinical classification of LE.
5. Name the typical clinical manifestations of LE.
6. Make a plan for laboratory and instrumental examination of patients with LE.
7. Indicate complications of LE.
9. Name the principles of treatment of LE.
10. Indicate the main groups of drugs used in the treatment of LE.

Tests for initial control:

1. (On a substitution, α=2). Basic factor in development of leukemia is_____.

Standard of answer: multistage formation leukemic clones.

2. (On a substitution and sequence, α =2). Name the key concepts in pathogenesis of leukemia in correct sequence:

Standard of answer:

1) lesions of hemopoesis on the level of hematopoietic stem cells polipotentnyh, violations cell proliferation while preserving differentiation;
2) violation of apoptosis, immune disorders;
3) violation of proliferation and differentiation in the bone marrow, the accumulation of masses of tumor cells;
4) inhibition of normal hemopoesis, leukemic infiltration of organs and tissues;
5) autoimmune and infectious-inflammatory complications.

3. (On a sequence, α =2). Set the faithful sequence of periods of leukemia:

1) preleukemia;
2) remission;
3) recurrence;
4) terminal;
5) acute.

Standard of answer: 1), 5), 2), 3), 4).

4. (With a plural choice, α=2). What groups of preparations are basic drugs according to management of patients with leukemia?

1) Alkaloids	6) Corticosteroids
2) Alkylating agents	7) Mineralocorticoids
3) Anticancer antimetabolites	8) NAIDs
4) Anthracyclines	9) Methylhydrazine derivatives
5) Vitamins	10) Urea derivatives

Standard of answer: 1), 2), 3), 4), 6), 9), 10).

5. (On accordance, α=2) Define accordance the groups of preparations to drugs used for treatment in patients with leukemia.

1) Methotrexate	A) Alkylating agents
2) Cyclophosphan	B) Anthracyclines
3) Prednisolone	C) Anticancer antimetabolites
4) Vinblastin	D) Urea derivatives
5) Adriamycin	E) Corticosteroids
6) Hydroxyurea	F) Alkaloids

Standard of answer: 1 -C; 2 - A; 3-E; 4 -F; 5 -B; 6 - D.

Tasks of II level:

1. For a patient after a quinsy pain appeared in tube bones, general increase of lymphonodes, hepatolienal syndrome. Blood test: RBC- 3,0*10^12/l, Hb – 80 g/L, L – 18*10^9/l, blasts- 90%, lymphocytes - 46%, thrombocytes – 50 10^9/l, ESR - 65 mm/h. Your diagnosis is:
   A. *Acute lymphoblastic leukemia
   B. Chronic lympholeukemia
   C. Chronic myeloleukemia
   D. Myeloma
   E. Acute myeloblastic leukemia.
2. In patient of 42 years old in 2 months after acute respiratory disease appeared a general weakness, subfebrility. The skin is pale, spleen is enlarged on 4 sm. FBC: RBC-2.9*10^12/l, Hb–90 g/L, WBC-3.3*10^9/l, blasts–31%, myelocytes 0.5%, metamyelocytes-0.5%, b-4%, s-32%, e-2%, lymph-22%, monocytes- 8%, platelets-60*10^9/l, ESR 25 mm/h. What is the initial diagnosis? What additional examination methods are necessary to prescribe?
   A. Acute leukemia, cytochemical examination
   B. Erythremia, hematocrit
   C. *Chronic myeloleukemia, bone marrow aspirate
   D. Chronic lympholeukemia, bone marrow aspirate
   E. Myeloma, blood biochemical analysis
3. Select the most characteristic clinical symptoms of the 2 stage of chronic lympholeukemia:
   A. Increase of lymphatic nodes
   B. Hemorrhagic syndrome
   C. Hemolytic crisis
   D. Splenohepatomegaly
   E. *All listed.
4. Patient of 19 years old. FBC: Hb – 50.0 g/L, RBC – 2.5 10^12/l, WBC – 4.2*10^9/l, blasts - 47%, segm. - 11%, monocytes - 10%, lymphocytes - 32%, platelets – 80.0*10^9/l. What primary additional examination methods are necessary for diagnosis?
   A. *Cytologic research of bone marrow
   B. Cumbs' test, liver function tests
   C. Proteinogram, coagulogram
   D. Electrolytes level in blood and urine
   E. Uric acid blood level.
5. In what leukemia a basophil -eosinophil association may be revealed?
   A. Acute myeloblastic
   B. *Chronic myeloleukemia
   C. Chronic lympholeukemia
   D. Erythremia
   E. Chronic erythromyelosis
6. What amount of blast cells in puncture material of bone marrow is acceptable in the period of clinico-hematological remission?
   A. 4%
   B. *5%
   C. 8%
   D. 10%
   E. 15%
7. What examination method is necessary to confirm a diagnosis of neuroleucemia?
   A. Bone marrow aspirate
   B. Trephine biopsy
   C. *Liquor test
   D. Computer tomography
   E. Blood test
8. What variant of acute leukemia is the most frequent in adults?
   A. Lymphoblastic
   B. *Myeloblastic

C. Monoblastic
D. Undifferentiated
E. Promyelocytic

9. What laboratory sign is the main in diagnostics of acute leukemia?
A. Leucopenia
B. Leucocytosis
C. Anemia
D. Thrombocytopenia
E. *Blastemia

10. At what disease blast cells and “hiatus leucemicus” are revealed in a full blood count?
A. Chronic myeloleukemia
B. Chronic lympholeukemia
C. Lymphogranulematosis
D. Myeloma
E. *Acute leukemia

11. What changes of peripheral blood are characteristic for chronic lympholeukemia?
A. Leucopenia
B. Eosinophilia
C. Lymphopenia
D. *Leucocytosis, absolute lymphocytosis
E. All invalid.

12. Systemic enlargement of lymphatic nodes is characteristic for:
A. Hypoplastic anemia
B. Myeloma
C. Rendu-Osler-Weber 's disease
D. Addison-Biermer's anemia
E. *Chronic lympholeukemia.

VII.2 Materials of the methodical providing of the basic stage of lesson

Professional algorithm of curation of patient (reference card) for forming of practical skills and abilities

№	Task	Sequence execution	Notes, warnings on self-control
1	*2*	*3*	*4*
1	To conduct the objective inspection of patient with leukemia	1. To conduct collection of complaints, anamnesis of disease. 2. Carefully to collect anamnesis of life of patient. 3. To conduct a review patient. 4. To investigate the cardiovascular system of the patient (palpation, percussion).	Pay attention to the features, characteristics of pain syndrome. Set risk factors and comorbidities lead to LE. Estimate the general state the patient, position in bed, color and moisture of the skin and mucous membranes. Reveal pale, moist skin, cyanosis of lips. Pay attention to the rhythm of the pulse, presence pulse deficit, its tension and size on both hands, apical, its properties, limits of absolute and relative cardiac dullness, their changes in heart rate (tachy- or bradycardia, extrasystoles), BP (increase then decrease SBP)
		5. Conduct heart auscultation and great vessels. 6. Conduct auscultation of the lungs. 7. To investigate the digestive system.	Pay attention to the decreased I tone, III, IV tones. Set the presence of dyspnea, rales. Identify pain zones, hepatosplenomegaly.

2	To formulate a previous diagnosis.	1. Formulate and preliminary diagnosis. 2. Substantiate all components of previous diagnosis on the basis of complaints, medical history and life, physical examination	Based on the current classification of LE formulate a preliminary diagnosis and substantiate every component.
3	To estimate the indexes of additional laboratory researches.	1. To estimate full blood count. 2. To estimate myelogram.	To pay attention in the presence of lecocytosis, blastemia, changes of leukoformula, "hiatus leukemicus", pancytopenia, increased ESR.
4	To interpret information of additional instrumental researches.	1. To interpret FGDS, colonoscopy, abdominal sonogram.	To pay attention on pathology leads to bleeding, hepatosplenomegaly, lymphadenopathy.
5.	To conduct differential diagnostics.	1. Consistently find similarities in the complaints, medical history of the disease and life, objective status, data, laboratory and instrumental methods of examination of the patient and with similar nosology. 2. Find the differences between the complaints, according to medical history and life, objective symptoms, results of laboratory and instrumental methods of research and patient with similar nosology. 3. Based on the identified differences exclude similar disease from the list of possible diagnoses. 4. To the differential diagnosis by the aforementioned algorithm with all nosology that have similar clinical signs with the patient. 5. Given the impossibility to exclude anemia from a list of possible diagnoses draw a conclusion the greatest likelihood of such a diagnosis.	Particular attention should be paid to the differential diagnosis of leukemoid reactions, aplastic anemia, cancer, lymphomas, hemophilia, thrombocytopenia
6.	To formulate a final clinical diagnosis.	1. Formulate a final clinical diagnosis. 2. Based on the diagnosis, analysis of additional laboratory and instrumental methods conducted differential diagnosis to justify all the elements of the final clinical diagnosis.	Based on the current classification of LE formulate previous diagnosis indicating the stage and severity of exacerbations, complications of the underlying disease and concomitant diseases.
7.	To administer	1. Life style recommendations. 2. To administer drugs, other	To indicate the regime and diet. Considering the age, the severity of disease, presence of

	treatment a patient.	methods of treatment.	complications and concomitant pathology appoint modern medical treatment according to the LE guidelines.

VII.3 Materials of control for the final stage of lesson

Tests of III level (α=3).

Male, 18 y.o. One month ago he had ARVI and used amoxicillin and sulfadimethoxine. During last week he had been suffering from sore throat, pain in gums, fever to 39 ^{o}C. Exam: patient is pale, tongue – dry. There are gingival, palatal necrotic ulcers had a dirty-grey fur on them; necrotic tonsillitis. CBC: Er. 3,2x10^12/l, Hb-100 g/l, Leuc.-80x10^9/l, segm.-22%, mon.-3%, blasts-75%, ESR-65 mm/h.

1) What is initial diagnosis?
2) What tests the patient needs?
3) What tactic of management?

Standard of answer:

1) Acute leukemia.
2) Bone marrow aspiration, cytochemical and cytogenetic studies.
3) Conventional induction therapy: polychemotherapy.

VIII. Materials of the methodical providing of self-study of students: a reference card is for organization of independent work of students with educational literature

Task	Instructions
To learn etiology of LE	List the basic etiologic factors of LE
To learn pathogenesis of LE	To select the key links of pathogenesis of LE
To learn the clinical manifestation of LE	To set symptoms and clinical syndromes which enable to offer the previous diagnosis of LE
To learn the diagnostic criteria of LE	To make the structural scheme of disease
To learn the investigation (laboratory, instrumental)	To make a plan of examination of patient with LE
To learn specific changes of images and analyses at LE	List the basic diagnostic criteria of LE according to data of investigations
To conduct differential diagnostics, set a final clinical diagnosis	Substitute the basic components of diagnosis in accordance with modern classification, and to conduct a differential diagnosis
To administer the individual treatment patient with LE	Wright down the list of prescriptions include the regime, diet, drug therapy considering the age, the severity of disease, presence of complications and concomitant pathology

THEME 27

LYMPHOMAS AND MULTIPLE MYELOMA.

Studying time: 5 hours.

I. Actuality of theme. "Lymphoma" is a general term for many blood cancers that originate in the lymphatic system. Lymphoma results when a lymphocyte (a type of white cell) undergoes a malignant change and multiplies out of control. Eventually, healthy cells are crowded out and malignant lymphocytes amass in the lymph nodes, liver, spleen and/or other sites in the body. An estimated total of 731,277 individuals in the US population are living with, or in remission from, lymphoma.

Hodgkin lymphoma (HL) (formerly, Hodgkin disease) is a potentially curable lymphoma with distinct histology, biologic behavior, and clinical characteristics. Thomas Hodgkin first described the disorder in 1832; in the 20th century, realization that the disease is a lymphoid malignancy led to it being renamed Hodgkin lymphoma. HL represents 11.8 percent of all types of lymphoma diagnosed in 2013. This disease has characteristics that distinguish it from other diseases classified as lymphoma, including the presence of the Reed-Sternberg cell, a large, malignant cell found in lymphoma tissues. The crude incidence of HL in the European Union is 2.2 and the mortality is 0.7 cases/100 000/year.

Non-Hodgkin lymphoma (NHL) represents a diverse group of diseases that are distinguished by the characteristics of the cancer cells associated with each disease type. The designations "indolent" and "aggressive" are often applied to types of NHL. Each type is associated with factors that categorize the prognosis as either more or less favorable. NHL is the sixth most common cause of cancer deaths in males and the seventh in females. The age-adjusted incidence of NHL rose by 89.5 percent from 1975 to 2010, an average annual percentage increase of 2.6 percent.

Myeloma is a cancer of the plasma cells. About 90 percent of people with myeloma have disease involving multiple sites at the time of diagnosis. Some individuals have myeloma that progresses very slowly (sometimes referred to as "smoldering" or "indolent" myeloma). An estimated 22,350 new cases of myeloma (12,440 males and 9,910 females) are expected to be diagnosed in the US in 2013. The incidence rate for the years 2006 to 2010 was 56.3 percent higher in males (7.5 per 100,000 population) than in females (4.8 per 100,000 population).

II. Purposes of lesson.

Student must know (α1, 2):

- classification of malignant neoplasms of lymphoid (MNL);
- clinical presentation of Hodgkin lymphoma (HL) and non-Hodgkin lymphomas (NHL);
- exams and tests for diagnostics and differential diagnostics of MNL;
- principles of treatment of MNL;
- clinical presentation, exams and tests for diagnostics of Multiple myeloma (MM);
- principles of treatment of MM;
- clinical presentation, exams and tests for diagnostics of NHL;
- principles of treatment of NHL.

Student should be able to (α 3):

- Substantiate the diagnosis MM according to data of exams and tests;
- Substantiate the diagnosis HL and NHL according to data of exams and tests;
- At differential diagnostics choose typical signs for ever nosology (algorithmic principle);
- Write down case history and list of prescriptions;
- Recognize signs of MM, MNL in the bone marrow and peripheral blood slides.

Students must acquire the skills (α 3):

- Conduct examination of patient with MM (history taking, view, physical exam);
- Conduct examination of patient with HL (history taking, view, physical exam);
- Conduct examination of patient with NHL (history taking, view, physical exam);
- To interpret laboratory and instrumental data to diagnose MM, HL, NHL;
- To choose tactic of management and treatment of patients with HL, NHL and MM.

III. Goals the development of personality (educational goals).

- The student must learn to follow the rules of conduct, principles of medical ethics and deontology bedside with HL, NHL and MM;

- Possess the ability to establish psychological contact with the patient and his family;
- Acquires a sense of professional responsibility for the timeliness and adequacy of quality medical care.

IV. Interdisciplinary integration.

Discipline	To know	To be able to
1	*2*	*3*
1. Previous (providing)		
Normal anatomy	The structure of human hemopoesis, its blood supply and innervation	
Histology	Blood cells	To estimate normal blood count and at pathology
Normal physiology	Physiology of blood system, normative indices of laboratory and instrumental methods of investigation, their value	To estimate results of investigations of blood system
Pathological physiology	Key links of pathogenesis of MM, HL, NHL	
Pathological anatomy	Morphological features of development of MM, HL, NHL	To analyze and interpret data of clinical inspection and investigation of patient
Pharmacology	Pharmacokinetics, pharmacodynamics, side effects of drugs used in the treatment of patients with MM, HL, NHL	Assign treatment, depending on age and individual characteristics of the patient, disease period. Define the optimal mode of reception and administration of drugs. Write recipes.
Propedeutics Internal Medicine	Basic stages and methods of clinical examination of the patient	Collect complaints, medical history, history of life, identify the main risk factors for MM, HL, NHL, conduct an objective examination of the patient's organs and systems, to identify the clinical features of anemia, interpret these additional laboratory and instrumental studies
Radiation diagnostics	Normative indices of abdominal and bones X-ray, CT-scan and US in MM, HL, NHL	Interpret data of X-ray and CT images, sonograms
Neurology	Neurological syndromes	Estimate neurological symptoms and take differential diagnostics with clinical manifestation of MM, HL, NHL
2. Followings (provided)		
Emergency states	Risk factors and clinical manifestations of urgent conditions in patients with MM, HL, NHL	Render first aid in emergency conditions in patients with MM, HL, NHL
Hospital therapy	Clinical manifestation of complications and atypical forms of MM, HL, NHL, tactic of treatment	To determine the clinical displays of complications and atypical forms of MM, HL, NHL, able to administer treatment
3. Interdisciplinary integration		
Leukemia	Clinical manifestations of acute and chronic leukemia	Establish the characteristic clinical signs of leukemia and to perform differential diagnosis of MM, HL, NHL
Hepatolienal syndrome	Clinical manifestations of hepatolienal syndrome	Establish the characteristic clinical signs of hepatolienal syndrome and to perform differential diagnosis of MM, HL, NHL
Aplastic anemia	Clinical manifestations of anemia	Establish the characteristic clinical signs of aplastic anemia and to perform differential diagnosis of MM, HL, NHL
Hemorrhagic syndromes	Clinical manifestations of hemophilia, thrombocytopenia, Schönlein-Henoch disease	Establish the main clinical signs of hemorrhagic syndromes and to perform differential diagnosis of MM, HL, NHL

Renal failure	Clinical manifestations of kidney disorders	Establish the characteristic clinical signs of kidney disorders and to perform differential diagnosis of MM, HL, NHL
Rheumatoid arthritis	Clinical manifestations of rheumatoid arthritis	To determine the clinical signs of rheumatoid arthritis and to conduct differential diagnostics with MM, HL, NHL

V. Table of contents of theme of lesson

Classification of lymphomas and multiple myeloma, ICD-10.

Malignant neoplasms of lymphoid, hematopoietic and related tissue C81-C96

- C81 Hodgkin lymphoma
- C82 Follicular lymphoma
- C83 Non-follicular lymphoma
- C84 Mature T/NK-cell lymphomas
- C85 Other specified and unspecified types of non-Hodgkin lymphoma
- C86 Other specified types of T/NK-cell lymphoma
- C88 Malignant immunoproliferative diseases and certain other B-cell lymphomas
- C90 Multiple myeloma and malignant plasma cell neoplasms
- C91 Lymphoid leukemia
- C92 Myeloid leukemia
- C93 Monocytic leukemia
- C94 Other leukemias of specified cell type
- C95 Leukemia of unspecified cell type
- C96 Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue

C81 Hodgkin lymphoma

- 81.0Nodular lymphocyte predominant Hodgkin lymphoma
  - ✓ C81.1Nodular sclerosis classical Hodgkin lymphoma
  - ✓ C81.2Mixed cellularity classical Hodgkin lymphoma
  - ✓ C81.3Lymphocyte depleted classical Hodgkin lymphoma
  - ✓ C81.4Lymphocyte-rich classical Hodgkin lymphoma
- C81.7Other classical Hodgkin lymphoma
- C81.9Hodgkin lymphoma, unspecified

Multiple myeloma and malignant plasma cell neoplasms C90

- C90.0 Multiple myeloma
- C90.00not having achieved remission
- C90.01in remission
- C90.02 in relapse

HODGKIN LYMPHOMA

The results of certain studies about causes of Hodgkin lymphoma (HL) have not been definitive - many studies of links between HL and environmental exposures have been conducted, with unclear results. Although Epstein-Barr virus (EBV) has been associated with nearly half of HL cases, EBV has not been conclusively established as a cause. Almost 100% of HIV-associated cases are EBV-positive. An epidemiologic study from Denmark and Sweden showed an increased risk of EBV-positive Hodgkin lymphoma in patients with a self-reported history of infectious mononucleosis in adolescence. The average incubation time from IM to symptoms of HL was 2.9 years. Genetic predisposition may play a role in the pathogenesis of HL. Approximately 1% of patients with Hodgkin lymphoma have a family history of the disease. Siblings of an affected individual have a 3- to 7-fold increased risk for developing Hodgkin lymphoma. This risk is higher in monozygotic twins. Human leukocyte antigen (HLA)-DP alleles are more common in Hodgkin lymphoma.

A study by Chang et al found that routine residential UV radiation exposure may have a protective effect against lymphomagenesis through mechanisms that may be independent of vitamin D. Most cases of HL occur in people who do not have identifiable risk factors; most people with identifiable risk factors do

not develop HL.

HL ***classified by the WHO*** into 5 types. Of these, 4- nodular sclerosis, mixed cellularity, lymphocyte depleted, and lymphocyte rich—are referred to as classic Hodgkin lymphoma and represents≈95% of all HL cases; the fifth type, nodular lymphocyte predominant Hodgkin disease (NLPHD) which accounts for ≈5% of all HL cases.

In classic Hodgkin lymphoma, the neoplastic cell is the Reed-Sternberg (RS) cell. RS cells comprise only 1-2% of the total tumor cell mass. The remainder is composed of a variety of reactive, mixed inflammatory cells consisting of lymphocytes, plasma cells, neutrophils, eosinophils, and histiocytes.

Most RS cells are of B-cell origin, derived from lymph node germinal centers but no longer able to produce antibodies. Some Hodgkin lymphoma cases have been identified in which the RS cell is of T-cell origin but these are rare, accounting for 1-2% of classic Hodgkin lymphoma.

The RS cells consistently express the CD30 (Ki-1) and CD15 (Leu-M1) antigens. CD30 is a marker of lymphocyte activation that is expressed by reactive and malignant lymphoid cells and was originally identified as a cell surface antigen on RS cells. CD15 is a marker of late granulocytes, monocytes, and activated T cells that is not normally expressed by cells of B lineage.

Nodular sclerosis. In nodular sclerosis HL, which constitutes 60-80% of all cases of it, the morphology shows a nodular pattern. Broad bands of fibrosis divide the node into nodules. The capsule is thickened. The characteristic cell is the lacunar-type Reed-Sternberg cell, which has a monolobated or multilobated nucleus, a small nucleolus, and abundant pale cytoplasm. It is frequently observed in adolescents and young adults. It usually involves the mediastinum and other supradiaphragmatic sites.

Mixed-cellularity. In mixed-cellularity HL (MCHL), which constitutes 15-30% of cases, the infiltrate is usually diffuse. RS cells are of the classic type (large, with bilobate, double or multiple nuclei, and a large, eosinophilic nucleolus). MCHL commonly affects the abdominal lymph nodes and spleen. Patients with this histology typically have advanced-stage disease with systemic symptoms. MCHL is the histologic type most commonly observed in patients with HIV infection.

Lymphocyte-depleted. Lymphocyte-depleted HL (LDHL) constitutes less than 1% of cases. The infiltrate in LDHL is diffuse and often appears hypocellular. Large numbers of Reed-Sternberg cells and bizarre sarcomatous variants are present. LDHL is associated with older age and HIV-positive status. Patients usually present with advanced-stage disease. EBV proteins are expressed in many of these tumors. Many cases of LDHL diagnosed in the past were actually were non-Hodgkin lymphomas, often of the anaplastic large-cell type.

Lymphocyte-rich classic HL (LRHL) constitutes 5% of cases. In LRHL, RS cells of the classic or lacunar type are observed, with a background infiltrate of lymphocytes. It requires immunohistochemical diagnosis. Some cases may have a nodular pattern. Clinically, the presentation and survival patterns are similar to those for MCHL.

Nodular lymphocyte-predominant HL (NLPHL) constitutes 5% of cases. In contrast to the other histologic subtypes, the typical RScells are either infrequent or absent in NLPHL. Instead, lymphocytic and histiocytic (L&H) cells, or "popcorn cells" (their nuclei resemble an exploded kernel of corn), are seen within a background of inflammatory cells, which are predominantly benign lymphocytes. Unlike Reed-Sternberg cells, L&H cells are positive for B-cell antigens, such as CD19 and CD20, and are negative for CD15 and CD30. A diagnosis of NLPHD needs to be supported by immunohistochemical studies, because it can appear similar to LRHL or even some non-Hodgkin lymphomas.

The Ann Arbor classification for staging HL is as follows:

- Stage I - Single lymph node area or single extranodal site.
- Stage II - 2 or more lymph node areas on the same side of the diaphragm.
- Stage III - Lymph node areas on both sides of the diaphragm.
- Stage IV - Disseminated or multiple involvement of the extranodal organs.

Descriptive suffixes that may be added to the stages include the following:

- ✓ S – Splenic involvement
- ✓ B – Presence of B symptoms (temperature >38°C, drenching night sweats, unexplained loss of >10% of body weight in the preceding 6 months)
- ✓ A – Absence of B symptoms
- ✓ X – Presence of bulky disease
- ✓ E – Contiguous involvement of extranodal sites

In patients with stage I or II disease, the following factors are considered unfavorable:

- Bulky disease.
- ESR ≥50 mm/hr if the patient is otherwise asymptomatic.
- >3 sites of disease involvemen.t
- Presence of B symptoms.
- Presence of extranodal disease.

In patients with advanced disease, the following factors are considered unfavorable:

- Serum albumin < 4 g/dL.
- Hemoglobin < 10.5 g/dL.
- Male sex.
- Stage IV disease.
- Age ≥45 years.
- White blood cell (WBC) count >15,000/μL.
- Lymphocyte count < 600/μL or < 8% of total WBC count.

Signs and Symptoms

- Painless enlargement of one or more lymph nodes (above the diaphragm in 80% of patients).
- Constitutional symptoms (40% of cases; collectively known as "B symptoms").
- Intermittent fever (~35% of cases); classic Pel-Ebstein fever (infrequent).
- Chest pain, cough, shortness of breath.
- Pain at nodal disease sites, precipitated by drinking alcohol (< 10% of cases but specific for Hodgkin lymphoma).
- Back or bone pain (rare).
- Persistent cough and shortness of breath; or a combination thereof; hemoptysis (rare).
- Drenching night sweats of the whole body.
- Itching.
- Weight loss.

Physical findings in HL are as follows:

- Palpable, painless lymphadenopathy (rubbery adenopathy) in the neck (60-80%), axilla (6-20%), or groin (6-20%).
- Involvement of the Waldeyer ring or occipital or epitrochlear areas (infrequent).
- Splenomegaly or hepatomegaly.
- Superior vena cava syndrome (in patients with massive mediastinal lymphadenopathy).
- Central nervous system signs due to paraneoplastic syndromes.

Exams and Tests

Pathological diagnosis should be made according to the WHO classification from a sufficiently large surgical specimen or excisional lymph node biopsy to provide enough material for fresh frozen and formalin-fixed samples.

Blood studies may include the following:

- Full blood cell count.
- Blood chemistry: glucose, alkaline phosphatase, lactate dehydrogenase, liver enzymes, albumin and thyroid-stimulating hormone, electrolytes glucose, cytokines (usually only in special situations or in the context of a clinical trial).
- Screening for hepatitis B (HBV), hepatitis C (HCV) and human immunodeficiency virus (HIV).

Instrumental studies may include the following:

- Chest X-ray and a CT scan of neck, chest and abdomen.
- Bone marrow aspiration and histology.
- Positron emission tomography.
- Cardiac and pulmonary function tests.

Treatment

Cure is the goal of treatment for people who have HL. "Involved field" radiation therapy with chemotherapy (sometimes called "combined modality therapy") has been the most common treatment approach for HL. Involved field radiation therapy targets the evident HL cell masses, and chemotherapy is used to kill

neighboring lymphoma cells. Clinical trials are under way comparing chemotherapy with radiation to chemotherapy-only to treat patients with stage IA and IIA nonbulky HL.

Staging is carried out according to the Ann Arbor system in consideration of the risk factors listed in Table 1. After completion of staging, patients are allocated and treatment is chosen according to three categories (limited, intermediate or advanced stages).

Table 1.

Treatment group	EORTC/GELA	GHSG
Limited stage patients	CS I–II without risk factors (supradiaphragmatic)	CS I–II without risk factors (supradiaphragmatic)
Intermediate stage patients	CS I–II with ≥1 risk factors (supradiaphragmatic)	CS I, CS IIA with ≥1 risk factors; CS IIB with risk factors C/D, but not A/B
Advanced stage patients	CS III–IV	CS IIB with risk factors A/B CS III/IV
Risk factors	(A) large mediastinal mass[a] (B) age≥50 years (C) elevated ESR[b] (D) ≥4 nodal areas	(A) large mediastinal mass[a] (B) extranodal disease (C) elevated ESR (D) ≥3 nodal areas

[a] Large mediastinal mass: more than one-third of the maximum horizontal chest diameter.
[b] ESR: >50 mm/h without B-symptoms, >30 mm/h with B-symptoms (B-symptoms: fever, night sweat, weight loss).
CS (clinical stage); EORTC (European Organisation for Research and Treatment of Cancer); GELA Groupe d'Etude des Lymphomes de l'adulte); GHSG (German Hodgkin Study Group).

Combined modality treatment consisting of a brief chemotherapy followed by radiotherapy was shown to result in superior tumor control compared with radiotherapy alone. Currently, two or three cycles of adriamycin/bleomycin/vinblastine/dacarbazine (ABVD) (Table 2) followed by involved-field radiotherapy (IF-RT) are considered standard of care for ***limited stage HL*** (D. A. Eichenauer, 2011). Recently, the final analysis of a large multicenter trial in which patients were randomly assigned to either two or four cycles of ABVD followed by either 20 Gy or 30 Gy IF-RT was performed. As a result, patients of all treatment groups had similar freedom from treatment failure (FFTF) and overall survival (OS) rates so that the least toxic approach consisting of two cycles of ABVD followed by 20 Gy IF-RT appears to be sufficient in limited stage HL.

Table 2.The ABVD regimen

Adriamycin	25 mg/m2 i.v.	Days 1 + 15
Bleomycin	10 mg/m2 i.v.	Days 1 + 15
Vinblastine	6 mg/m2 i.v.	Days 1 + 15
Dacarbazine	375 mg/m2 i.v.	Days 1 + 15

Recycle: day 29.

Intermediate stage HL is usually treated with combined modality approaches. Four cycles of ABVD followed by 30 Gy IF-RT are widely considered standard for intermediate stage HL [I, A] (D. A. Eichenauer, 2011). In patients up to 60 years who are eligible for a more intensive treatment, this standard is currently challenged by a protocol consisting of two cycles of bleomycin/etoposide/adriamycin/ cyclophosphamide/vincristine/procarbazine/prednisone in escalated dose (BEACOPPescalated) (Table 3) followed by two cycles of ABVD and 30 Gy IF-RT. At 4 years, FFTF with this new protocol was superior in comparison with four cycles of ABVD followed by 30 Gy IF-RT. However, long term results including data on possible late toxicity (e.g.infertility) associated with the regimen are lacking.Similar to limited stage HL, the question of whether radiotherapy is dispensable in selected patients cannot be answered yet. Ongoing trials are evaluating whether treatment might be stratified on the basis of FDG-PET, but none of the trials has been finally analyzed.

Table 3. The BEACOPPescalated regimen

Bleomycin	10 mg/m2 i.v.	Day 8
Etoposide	200 mg/m2 i.v.	Days 1–3
Adriamycin	35 mg/m2 i.v.	Day 1
Cyclophosphamide	1250 mg/m2 i.v.	Day 1

Vincristine	1,4 mg/m2, max. 2 mg i.v.	Day 8
Procarbazine	100 mg/m2 p.o.	Day 1–7
Prednisone	40 mg/m2 p.o.	Day 1–14
G-CSF	s.c.	From day 8

Advanced stage HL is usually treated with chemotherapy alone (D. A. Eichenauer, 2011). Radiotherapy is confined to patients having large residual masses after chemotherapy. Patients up to 60 years old are treated with either six (patients with complete remission after four cycles) or eight (patients with partial remission after four cycles) cycles of ABVD or eight cycles of BEACOPPescalated followed by a localized radiation with 30 Gy to residual lymphoma >1.5 cm [I–II, A]. However, recent analyses indicate that radiotherapy might be omitted in patients with residual lymphoma and a negative FDG-PET after completion of chemotherapy. In comparison with ABVD, treatment with BEACOPPescalated leads to superior FFTF and OS rates but is associated with an increased toxicity requiring granulocyte colony-stimulating factor (G-CSF) support. Patients older than 60 years should be treated with 6–8 cycles (depending on the remission status after four cycles) of ABVD followed by a localized radiation with 30 Gy to residual lymphoma >1.5 cm. The BEACOPP regimen should not be used in elderly patients since increased toxicity was observed in this age group [I–II, A].Ongoing trials are aimed at reducing treatment intensity without compromising efficacy. In most trials, interim FDGPET is used to distinguish between those patients who can potentially be cured with reduced therapy and those who require standard or even more intensive treatment. This approach seems promising since some trials suggest that interim FDG-PET is a good predictor for treatment failure in patients with advanced HL treated with ABVD. However, treatment stratification on the basis of interim FDG-PET cannot be considered standard yet, and further evidence from randomized trials is necessary

HL is now considered to be one of the most curable forms of cancer. The five-year relative survival rate for people with HL has more than doubled, from 40 percent in whites from 1960 to 1963 to 87.6 percent for all races from 2003 to 2009. The five-year relative survival rate is 93.5 percent for all people with HL who were less than 45 years old at diagnosis.

NONHODGKIN LYMPHOMA

The term lymphoma describes a heterogeneous group of malignancies with different biology and prognosis. In general, lymphomas are divided into 2 large groups of neoplasms, namely non-Hodgkin lymphoma (NHL). About 85% of all malignant lymphomas are NHLs. The median age at diagnosis is the sixth decade of life, although Burkitt lymphoma and lymphoblastic lymphoma occur in younger patients. NHL includes many clinicopathologic subtypes, each with distinct epidemiologies; etiologies; morphologic, immunophenotypic, genetic, and clinical features; and responses to therapy.

Currently, several NHL classification schemas exist, reflecting the growing understanding of the complex diversity of the NHL subtypes. The Working Formulation, originally proposed in 1982, classified and grouped lymphomas by morphology and clinical behavior (ie, low, intermediate, or high grade). In the 1990s, the Revised European-American Lymphoma (REAL) classification attempted to apply immunophenotypic and genetic features in identifying distinct clinicopathologic NHL entities. The WHO classification further elaborates upon the REAL approach. This classification divides NHL into those of B-cell origin and those of T-cell and natural killer (NK)–cell origin.

Etiology. The reasons for the development of NHL are not known. Chromosomal translocations and molecular rearrangements play an important role in the pathogenesis of many lymphomas and correlate with histology and immunophenotype. The t(14;18)(q32;q21) translocation is the most common chromosomal abnormality associated with NHL. This translocation occurs in 85% of follicular lymphomas and 28% of higher-grade NHLs. This translocation results in the juxtaposition of the bcl -2 apoptotic inhibitor oncogene at chromosome band 18q21 to the heavy chain region of the immunoglobulin (Ig) locus within chromosome band 14q32Immune suppression plays a role in some cases.

Some viruses are implicated in the pathogenesis of NHL, probably because of their ability to induce chronic antigenic stimulation and cytokine dysregulation, which leads to uncontrolled B- or T-cell stimulation, proliferation, and lymphomagenesis. EBV is a DNA virus that is associated with Burkitt lymphoma (especially the endemic form in Africa), Hodgkin disease, lymphomas in immunocompromised patients (eg, from HIV infection, organ transplantation), and sinonasal lymphoma. Human T-cell leukemia

virus type 1 causes a latent infection via reverse transcription in activated T-helper cells. This virus is endemic in certain areas of Japan and the Caribbean islands, and approximately 5% of carriers develop adult T-cell leukemia or lymphoma. HCV is associated with the development of clonal B-cell expansions and certain subtypes of NHL (ie, lymphoplasmacytic lymphoma, Waldenström macroglobulinemia), especially in the setting of essential (type II) mixed cryoglobulinemia. Kaposi sarcoma–associated herpesvirus is associated with body cavity–based lymphomas in patients with HIV infection and in patients with multicentric Castleman disease. Helicobacter pylori infection is associated with the development of primary gastrointestinal (GI) lymphomas, particularly gastric mucosa-associated lymphoid tissue (MALT) lymphomas.

Environmental factors linked to the development of NHL include chemicals (eg, pesticides, herbicides, solvents, organic chemicals, wood preservatives, dusts, hair dye), chemotherapy, and radiation exposure.

Congenital immunodeficiency states (severe combined immunodeficiency disease, Wiskott-Aldrich syndrome), acquired immunodeficiency states, and induced immunodeficiency states (immunosuppression) are associated with increased incidence of NHL and are characterized by a relatively high incidence of extranodal involvement, particularly of the GI tract, and with aggressive histology.

The chronic inflammation observed in patients with autoimmune disorders, such as Sjögren syndrome and Hashimoto thyroiditis, promotes the development of MALT and predisposes patients to subsequent lymphoid malignancies.

Pathophysiology. NHLs are tumors originating from lymphoid tissues, mainly of lymph nodes. Various neoplastic tumor cell lines correspond to each of the cellular components of antigen-stimulated lymphoid follicles. NHL represents a progressive clonal expansion of B cells or T cells and/or NK cells arising from an accumulation of lesions affecting proto-oncogenes or tumor suppressor genes, resulting in cell immortalization. These oncogenes can be activated by chromosomal translocations (ie, the genetic hallmark of lymphoid malignancies), or tumor suppressor loci can be inactivated by chromosomal deletion or mutation. In addition, the genome of certain lymphoma subtypes can be altered with the introduction of exogenous genes by various oncogenic viruses. Several cytogenetic lesions are associated with specific NHLs, reflecting the presence of specific markers of diagnostic significance in subclassifying various NHL subtypes. Almost 85% of NHLs are of B-cell origin; only 15% are derived from T/NK cells, and the small remainder stem from macrophages. These tumors are characterized by the level of differentiation, the size of the cell of origin, the origin cell's rate of proliferation, and the histologic pattern of growth.

For many of the B-cell NHL subtypes, the pattern of growth and cell size may be important determinants of tumor aggressiveness. Tumors that grow in a nodular pattern, which vaguely recapitulate normal B-cell lymphoid follicular structures, are generally less aggressive than lymphomas that proliferate in a diffuse pattern. Lymphomas of small lymphocytes generally have a more indolent course than those of large lymphocytes, which may have intermediate-grade or high-grade aggressiveness. However, some subtypes of high-grade lymphomas are characterized by small cell morphology.

The staging is established according to the Ann Arbor system (Table 4). For prognostic purposes, International Prognostic Index (IPI) and age-adjusted IPI (aa-IPI) should be calculated.

Table 4.The Ann Arbor staging classification.

I	Involvement of a single lymphatic region (I) or localized involvement of single extralymphatic organ or site (IE)
II	Involvement of two or more lymphatic regions on the same side of the diaphragm (II) or localized involvement of a single extralymphatic organ or site and of one or more lymphatic regions
III	Involvement of lymphatic regions on both side of the diaphragm.
IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without lymphatic involvement.

Signs and Symptoms

The clinical manifestations of NHL vary with such factors as the location of the lymphomatous process, the rate of tumor growth, and the function of the organ being compromised or displaced by the malignant process.

Signs and symptoms of low-grade lymphomas include the following:

- Peripheral lymphadenopathy: painless and slowly progressive; can spontaneously regress.
- Primary extranodal involvement and B symptoms (fever, night sweats, enlarged spleen, weight loss): uncommon at presentation; however, common with advanced, malignant transformation or end-stage disease.
- Bone marrow (: frequent involvement; may be associated with cytopenias; fatigue/weakness more common in advanced-stage disease.

Intermediate- and high-grade lymphomas including the following:

- Lymphadenopathy: most patients.
- Extranodal involvement: more than one third of patients; most common sites are GI/GU tracts (including Waldeyer ring), skin, bone marrow, sinuses, thyroid, CNS.
- B symptoms: Temperature >38°C, night sweats, weight loss >10% from baseline within 6 months; in approximately 30-40% of patients.

Some individuals may have no symptoms, and a diagnosis of NHL is made as a result of a periodic physical examination and testing.

Physical findings in NHL are as follows:

Low-grade lymphomas:

- peripheral adenopathy;
- splenomegaly;
- hepatomegaly.

Intermediate- and high-grade lymphomas:

- rapidly growing and bulky lymphadenopathy;
- splenomegaly;
- hepatomegaly;
- large abdominal mass: Usually in Burkitt lymphoma;
- testicular mass;
- skin lesions: associated with cutaneous T-cell lymphoma (mycosis fungoides), anaplastic large-cell lymphoma, and angioimmunoblastic lymphoma.

Exams and Tests

- CBC count: may be normal in early-stage disease; in more advanced stages, may demonstrate anemia, thrombocytopenia/leukopenia/pancytopenia, lymphocytosis, thrombocytosis.
- Serum chemistry studies: may show elevated LDH and calcium levels, abnormal liver function tests.
- Serum beta2-microglobulin level: may be elevated.
- HIV serology: especially in patients with diffuse large cell immunoblastic or small noncleaved histologies.
- Human T-cell lymphotropic virus-1 serology: for patients with adult T-cell leukemia/lymphoma.
- Hepatitis B testing: in patients in whom rituximab therapy is planned because reactivation has been reported.

Other tests that may be helpful in evaluating suspected NHL include the following:

- immunophenotypic analysis of lymph node, bone marrow, peripheral blood;
- cytogenetic studies: NHL occasionally associated with monoclonal gammopathy; possible positive Coombs test; may be hypogammaglobulinemia.

Imaging tests:

- ✓ Chest radiography.
- ✓ Upper GI series with small bowel follow-through: In patients with head and neck involvement and those with a GI primary lesion.
- ✓ CT scanning of the neck, chest, abdomen, and pelvis.
- ✓ PET scanning.
- ✓ Bone scanning: Only in patients with bone pain, elevated alkaline phosphatase, or both.

- ✓ Testicular ultrasonography: For opposite testis in male patients with a testicular primary lesion.
- ✓ Multiple gated acquisition scanning: For patients being considered for treatment with anthracyclines.
- ✓ MRI of brain/spinal cord: For suspected primary CNS lymphoma, lymphomatous meningitis, paraspinal lymphoma, or vertebral body involvement by lymphoma.

The diagnosis of NHL relies on pathologic confirmation following appropriate tissue biopsy. The following are procedures in cases of suspected NHL:

- Bone marrow aspiration and biopsy: for staging rather than diagnostic purposes.
- Excisional lymph node biopsy (extranodal biopsy): for lymphoma protocol studies.

Perform lumbar puncture for CSF analysis in patients with the following conditions:

- Diffuse aggressive NHL with bone marrow, epidural, testicular, paranasal sinus, or nasopharyngeal involvement, or 2 or more extranodal sites of disease
- High-grade lymphoblastic lymphoma.
- High-grade small noncleaved cell lymphomas.
- HIV-related lymphoma.
- Primary CNS lymphoma.
- Neurologic signs and symptoms.

Treatment

In general, the goal of treatment for NHL is to destroy as many lymphoma cells as possible and to induce a complete remission. Treatment protocols vary according to the type of disease. Chemotherapy and radiation therapy are the two principal forms of treatment. Although radiation therapy is not often the sole or principal curative therapy, it is an important additional treatment in some cases. Stem cell transplantation and a watch-and-wait strategy are also used to treat some NHL subtypes. Immunotherapy is indicated to treat individuals with specific types of NHL.

Treatment strategies should be stratified according to age, age adjusted IPI and feasibility of dose-intensified approaches (Table 5). In cases with high tumor load, precautions, as example by administering prednisone 100 mg p.o. several days as 'prephase' treatment, are required to avoid tumor lysis syndrome. Dose reductions due to hematological toxicity should be avoided. Febrile neutropenia justifies prophylactic use of hematopoietic growth factors in patients treated with curative intent and in all elderly patients.

Table 5. Recommended treatment strategies in diffuse large B-cell lymphoma

Young <61 years		
IPI low risk no bulk	*IPI low risk with bulk or IPI low-intermediate risk*	*IPI intermediate-high risk or IPI high risk*
R-CHOP21 × 6	R-ACVBP and sequential consolidation Or R-CHOP21 × 6 + IF-RT on bulk	R-CHOP21 × 8 or R-CHOP14 × 6 with 8 R Consider more intensive regimens: R-CHOEP14 × 6 or R-ACVBP plus HDCT with ASCT or R-dose-dense (R-CHOP14 like) plus R-HDCT with ASCT
Consider CNS prophylaxis in patients at risk for CNS progression		
Elderly >60 years		
Healthy	>80 years without cardiac dysfunction	UNFIT or FRAIL or >60 years with cardiac dysfunction
R-CHOP21 × 8 (R-CHOP21 × 6 for IPI low risk) or R-CHOP14 × 6 with 8 R	attenuated regimens: R-miniCHOP21 × 6	Doxorubicine substitution with etoposide or liposomal doxorubicine or others: R-C(X)OP21 × 6 or palliative care
Consider CNS prophylaxis in patients at risk		

First relapse/progress	
Eligible to transplant	Not eligible to transplant
Platinum-based chemotherapy regimens (i.e. R-DHAP, R-ICE) as salvage treatment	Platinum and/or gemcitabine-based regimens Clinical trials with novel drugs
For chemosensitive patients: R-HDCT with ASCT as remission consolidation	
Consider allogeneic transplantation in patients relapsed after R-HDCT with ASCT or in patients with poor risk factors at relapse	
>2 relapse/progress	
Eligible to transplant	Not eligible to transplant
Allogeneic transplantation	Clinical trials with novel drugs
Clinical trials with novel drugs	Palliative care

Young low-risk patients (aaIPI = 0) without bulky disease.

Six cycles of combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) treatment combined with six doses of rituximab given every 21 days is the current standard. Consolidation by radiotherapy to initial sites has proven no clear benefit.

Young low-intermediate-risk patients (aaIPI = 1) or IPI low risk (aaIPI = 0) with bulky disease.

R-CHOP 21 × 6 with radiotherapy to the sites of previous bulky disease was shown to be effective in this group of patients based on the results of the MINT study. Alternatively, an intensification of chemotherapy with RACVBP (rituximab, doxorubicin, vindesine, cyclophosphamide, bleomycin, and prednisolone given every 2 weeks followed by sequential consolidation) has been shown to improve survival when compared with eight cycles of R-CHOP in this category, but in this trial, radiotherapy was omitted in both arms. In this group of patients either RCHOP21 × 6 with radiotherapy to the sites of previous bulky disease or the intensified regimen R-ACVBP are recommended.

Young high and high-intermediate-risk patients (aaIPI ≥ 2).

There is no current standard in this subgroup. Thus, especially this patient population should be treated preferably in clinical trials. Six to eight cycles of chemotherapy with CHOP combined with eight doses of rituximab given every 21 days are most frequently applied. Dose-dense treatment with R-CHOP given every 14 days has not demonstrated survival advantage over standard R-CHOP given every 21 days overall. Recently, four randomized trials comparing R-HDC + ASCT versus R chemotherapy have been presented. Two trials show a PFS benefit for HDC with ASCT but no impact, at present, on survival, while two trials failed to demonstrate an improvement for the HDC arm. Therefore, HDC with ASCT in first line remains experimental in first-line therapy or may be suggested for selective high-risk patients. Consolidation by radiotherapy to sites of bulky disease has proven no benefit. The role of radiotherapy in partial remission remains to be established in patients treated with rituximab and evaluated with PET.

Patients aged 60–80 years.

Eight cycles of combination chemotherapy with CHOP treatment combined with eight doses of rituximab given every 21 days is the current standard. R-CHOP given every 14 days did not demonstrate survival advantage over RCHOP 21. If rituximab-CHOP is given every 14 days, six cycles of CHOP with eight cycles of rituximab are sufficient. In patients with localized disease, consolidation by radiotherapy has proven no benefit in patients treated prior the introduction of rituximab.

Patients aged >80 years

A comprehensive geriatric assessment is recommended to help determine choice of treatment in these patients. R-CHOP treatment could usually be used until 80 years of age in healthy patients. The combination of rituximab with attenuated chemotherapy, as R-miniCHOP, could induce complete remission and long survival in healthy patients older than 80 years. The doxorubicin substitution with etoposide or liposomal doxorubicin or even its omission can be considered from the beginning or after a few cycles in patients with cardiac dysfunction or otherwise unfit.

CNS prophylaxis.

Patients with high-intermediate and high-risk IPI, especially those with more than one extranodal site or elevated LDH are at higher risk of central nervous system (CNS) relapse. CNS prophylaxis should be recommended in this population but intrathecal injections of methotrexate are probably not an optimal method. Intravenous high-dose methotrexate associated with efficient disease control could be an interesting

alternative. Whether some specific involvement sites as paranasal sinus, upper neck or bone marrow should receive prophylaxis remains to be established. Testicular lymphoma must receive CNS prophylaxis.

The five-year relative survival rate for people with NHL has risen from 31 percent in whites from 1960 to 1963 to 71.2 percent for all races from 2003 to 2009.

MULTIPLE MYELOMA

Multiple myeloma (MM) is a debilitating malignancy that is part of a spectrum of diseases ranging from monoclonal gammopathy of unknown significance (MGUS) to plasma cell leukemia. First described in 1848, MM is characterized by a proliferation of malignant plasma cells and a subsequent overabundance of monoclonal paraprotein (M protein). An intriguing feature of MM is that the antibody-forming cells (ie, plasma cells) are malignant and, therefore, may cause unusual manifestations. MM accounts for 1% of all cancers and ~10% of all haematological malignancies. The incidence in Europe is 4.5–6.0/100 000/year with a median age at diagnosis of between 65 and 70 years; the mortality is 4.1/100 000/year.

The precise *etiology* of MM has not yet been established. Roles have been suggested for a variety of factors, including genetic causes, environmental or occupational causes, MGUS, radiation, chronic inflammation, and infection. MM has been reported in 2 or more first-degree relatives and in identical twins, although no evidence suggests a hereditary basis for the disease. Some studies have shown that abnormalities of certain oncogenes, such as c-myc, are associated with development early in the course of plasma cell tumors and that abnormalities of oncogenes such as N-ras and K-ras are associated with development after bone marrow relapse. Abnormalities of tumor suppressor genes, such as TP53, have been shown to be associated with spread to other organs.

Case-controlled studies have suggested a significant risk of developing MM in individuals with significant exposures in the agriculture, food, and petrochemical industries. An increased risk has been reported in farmers, especially in those who use herbicides and insecticides, and in people exposed to benzene and other organic solvents. Long-term (>20 y) exposure to hair dyes has been tied to an excessive risk of developing MM.

Approximately 19% of patients with MGUS develop MM within 2-19 years. A relationship between MM and preexisting chronic inflammatory diseases has been suggested. However, a case-control study provides no support for the role of chronic antigenic stimulation. Human herpesvirus 8 infection of bone marrow dendritic cells was found in patients with MM and in some patients with MGUS.

Pathophysiology. MM is characterized by neoplastic proliferation of plasma cells involving more than 10% of the bone marrow (see the images below). Increasing evidence suggests that the bone marrow microenvironment of tumor cells plays a pivotal role in the pathogenesis of myelomas. The malignant cells of MM, plasma cells, and plasmacytoid lymphocytes are the most mature cells of B-lymphocytes. B-cell maturation is associated with a programmed rearrangement of DNA sequences in the process of encoding the structure of mature immunoglobulins. It is characterized by overproduction of monoclonal immunoglobulin G (IgG), immunoglobulin A (IgA), and/or light chains, which may be identified with serum protein electrophoresis (SPEP) or urine protein electrophoresis (UPEP). The role of cytokines in the pathogenesis of MM is an important area of research. Interleukin (IL)–6 is also an important factor promoting the in vitro growth of myeloma cells. Other cytokines are tumor necrosis factor and IL-1b. The pathophysiologic basis for the clinical sequelae of MM involves the skeletal, hematologic, renal, and nervous systems, as well as general processes. Plasma-cell proliferation causes extensive skeletal destruction with osteolytic lesions, anemia, and hypercalcemia. Mechanisms for hypercalcemia include bony involvement and, possibly, humoral mechanisms. Isolated plasmacytomas (which affect 2-10% of patients) lead to hypercalcemia through production of the osteoclast-activating factor. Destruction of bone and its replacement by tumor may lead to pain, spinal cord compression, and pathologic fracture. The mechanism of spinal cord compression symptoms may be the development of an epidural mass with compression, a compression fracture of a vertebral body destroyed by multiple myeloma, or, rarely, an extradural mass. With pathologic fracture, bony involvement is typically lytic in nature.

Bone marrow infiltration by plasma cells results in neutropenia, anemia, and thrombocytopenia. In terms of bleeding, M components may interact specifically with clotting factors, leading to defective aggregation.

The most common mechanisms of renal injury in MM are direct tubular injury, amyloidosis, or involvement by plasmacytoma. Renal conditions that may be observed include hypercalcemic nephropathy,

hyperuricemia due to renal infiltration of plasma cells resulting in myeloma, light-chain nephropathy, amyloidosis, and glomerulosclerosis.

The nervous system may be involved as a result of radiculopathy and/or cord compression due to nerve compression and skeletal destruction (amyloid infiltration of nerves). General pathophysiologic processes include hyperviscosity syndrome. This syndrome is infrequent in MM and occurs with IgG1, IgG3, or IgA. MM may involve sludging in the capillaries, which results in purpura, retinal hemorrhage, papilledema, coronary ischemia, or central nervous system (CNS) symptoms (eg, confusion, vertigo, seizure). Cryoglobulinemia causes Raynaud phenomenon, thrombosis, and gangrene in the extremities.

Signs and Symptoms

The presentation of MM can range from asymptomatic to severely symptomatic, with complications requiring emergent treatment. Systemic ailments include bleeding, infection, and renal failure; pathologic fractures and spinal cord compression may occur.

Presenting symptoms of MM include the following:

- Bone pain.
- Pathologic fractures.
- Weakness, malaise.
- Bleeding, anemia.
- Infection (often pneumococcal).
- Hypercalcemia.
- Spinal cord compression.
- Renal failure.
- Neuropathies.

Physical examination for MM may reveal the following:

- HEENT examination: exudative macular detachment, retinal hemorrhage, or cotton-wool spots.
- Dermatologic evaluation: pallor from anemia, ecchymoses or purpura from thrombocytopenia; extramedullary plasmacytomas (most commonly in aerodigestive tract but also orbital, ear canal, cutaneous, gastric, rectal, prostatic, retroperitoneal areas).
- Musculoskeletal examination: bony tenderness or pain without tenderness.
- Neurologic assessment: sensory level change (ie, loss of sensation below a dermatome corresponding to a spinal cord compression), neuropathy, myopathy, positive Tinel sign, or positive Phalen sign.
- Abdominal examination: hepatosplenomegaly.
- Cardiovascular evaluation: cardiomegaly.

In patients with multiple myeloma and amyloidosis, the characteristic examination findings include the following:

- Shoulder pad sign.
- Macroglossia.
- Typical skin lesions.
- Postprotoscopic peripalpebral purpura.
- Carpal tunnel syndrome.
- Subcutaneous nodules.

Exams and Tests

- Complete blood cell count.
- Serum creatinine, calcium level, total protein, albumin and globulin, BUN, uric acid.
- 24-hour urine collection for quantification of the Bence Jones protein (ie, lambda light chains), protein, and creatinine clearance; proteinuria greater than 1 g of protein in 24 hours is a major criterion.
- C-reactive protein.
- Serum viscosity in patients with CNS symptoms, nosebleeds, or very high M protein levels.
- Serum and urine assessment for monoclonal protein (densitometer tracing and nephelometric quantitation; immunofixation for confirmation).
- Serum free light chain assay (in all patients with newly diagnosed plasma cell dyscrasias).
- ***Bone marrow aspiration and/or biopsy.***
- Serum beta2-microglobulin, albumin, and lactate dehydrogenase measurement.

- Standard metaphase cytogenetics.
- Fluorescence in situ hybridization.

Imaging tests:

- Simple radiography for the evaluation of skeleton lesions; skeletal survey, including the skull, long bones, and spine.
- MRI for detecting thoracic and lumbar spine lesions, paraspinal involvement, and early cord compression.
- PET scanning in conjunction with MRI potentially useful.

The diagnosis of symptomatic MM requires:

- ≥10% clonal plasma cells on BM examination or a biopsy proven plasmacytoma;
- evidence of end-organ damage, the so-called CRAB criteria (hypercalcaemia, renal insufficiency, anemia or bone lesions) that is felt to be related to the underlying plasma cell disorder.

Table 6. Diagnostic criteria for plasma cell disorders

Disorder	**Disease definition**
Monoclonal gammopathy of undetermined significance (MGUS)	All three criteria must be met: - Serum monoclonal protein <3 g/dl - Clonal BM plasma cells <10%, and - Absence of end-organ damage such as hypercalcaemia, renal insufficiency, anemia and bone lesions (CRAB) that can be attributed to the plasmacell proliferative disorder
Smouldering multiple myeloma (also referred to as asymptomatic multiple myeloma)	Both criteria must be met: - Serum monoclonal protein (IgG or IgA) ≥3 g/dl and/or clonal BM plasma cells ≥10%, and - Absence of end-organ damage such as lytic bone lesions, anemia, hypercalcaemia or renal failure that can be attributed to a plasma cell proliferative disorder
Multiple myeloma	**All criteria must be met:**
	- Clonal BM plasma cells ≥10% or biopsy proven plasmacytoma, and - Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically Hypercalcaemia: serum calcium >11.5 mg/dl or Renal insufficiency: serum creatinine >1.73 μmol/l (or >2 mg/dl) or estimated creatinine clearance <40 ml/min Anemia: normochromic, normocytic with a haemoglobin value of ≥2 g/dl below the lower limit of normal or a hemoglobin value <10 g/dl Bone lesions: lytic lesions, severe osteopenia or pathologic fractures

The course of MM is highly variable, and the clinical behavior is remarkably heterogeneous. Many studies have identified prognostic factors capable of predicting this heterogeneity in survival: serum β2-microglobulin, albumin, C-reactive protein and lactate dehydrogenase. The International Staging System (ISS), a powerful and reproducible three-stage classification (Table 7), relies on the combination of serum levels of β2-microglobulin and of albumin. ISS3 is associated with the poorest outcome. Cytogenetics, evaluated by FISH, is a major prognostic factor. Two recurrent genetic abnormalities, t (4;14) and deletion (17p), are mostly associated with a poorer outcome. Chromosome 1 abnormalities and t (14;16) are also adverse prognostic factors.

Table 7. International staging system.

Stage	Criteria
I	Serum β2M <3.5 mg/l and serum albumin ≥3.5 g/dl
II	Not stage I or III: serum β2 microglobulin <3.5 mg/l, but serum albumin <3.5 g/dl, and Serum β2 microglobulin 3.5–5.5 mg/l irrespective of the serum albumin

III	Serum β2M ≥5.5 mg/l

Treatment

The goals of treatment for people with myeloma are to reduce symptoms, to slow disease progression and to provide prolonged remissions. There have been significant treatment advances in recent years. The approach for treating each person is customized, based on the extent of disease and the rate of disease progression. People who have a slow-growing myeloma and no symptoms may not need treatment immediately. Some people need only supportive care to reduce symptoms of anemia, high blood calcium levels, infections and/or bone damage or osteoporosis. Patients who require myeloma-specific therapies may receive combination drug therapy, high dose chemotherapy with stem cell transplantation (autologous, allogeneic or reduced-intensity allogeneic), radiation therapy for local disease and/or new and emerging drug therapies as part of clinical trials.

Asymptomatic myeloma.

Immediate treatment is not recommended at the present time for patients with indolent myeloma.

Symptomatic myeloma.

Treatment should be initiated in all patients with active myeloma fulfilling the CRAB criteria, (hypercalcaemia >11.0 mg/dl), creatinine >2.0 mg/ml, anemia (Hb <10 g/dl), active bone lesions), and in those symptomatic due to the underlying disease.

Elderly patients (non-transplant setting). Oral combinations of melphalan and prednisone (MP) plus novel agents are considered as standards of care in Europe. The two following options are recommended based on data from randomised phase III trials: melphalan/prednisone/thalidomide (MPT), or bortezomib/melphalan/prednisone (VMP); both MPT and VMP are approved in this setting by the European Medicines Agency (EMA). Bendamustine plus prednisone is another regimen that is also approved by the EMA in patients who have clinical neuropathy at time of diagnosis precluding the use of thalidomide according to the MPT regimen or bortezomib according to the VMP regimen. Melphalan/prednisone/lenalidomide (MPR) has been evaluated in a prospective randomised study versus MP, but was not superior to the dual combination with a fixed number of cycles. This triplet combination is not approved and cannot be considered as a standard of care. Cyclophosphamide/thalidomide/dexamethasone (CTD) has also been compared with MP and is superior in terms of response rates, but does not induce a clear survival advantage over MP. Lenalidomide combined with low-dose dexamethasone, widely used in US centres, also yields important response and OS rates but is not approved in Europe. This regimen is currently being compared with MPT in a large randomized phase III trial.

Younger patients (<65 years or fit patients in good clinical condition). For patients in good clinical condition (e.g. fit patients), induction followed by high-dose therapy with autologous stem cell transplantation (ASCT) is the standard treatment. Response rates to induction therapy have been significantly increased by the use of novel agent based combinations. Bortezomib-dexamethasone, which is superior to the classical VAD regimen (vincristine, adriamycin and high-dose dexamethasone), has become thebackbone of induction therapy before ASCT. The addition of a third agent to bortezomib-dexamethasone, e.g. thalidomide (VTD), doxorubicin (DVD or PAD), lenalidomide (RVD) or cyclophosphamide (VCD), has shown higher response rates in phase II trials. Three prospective studies have already shown that VTD is superior to TD or bortezomib, dexamethasone. Melphalan (200 mg/m2 i.v.) is the standard preparative regimen before ASCT [II, B]. Peripheral blood progenitor cells are the preferred source of stem cells, rather than BM [III, B]. Tandem ASCT has been evaluated before the era of novel agents. The benefit of tandem ASCT was observed in patients that were not reaching very good partial response after the first ASCT.

Allogeneic stem cell transplantation should only be carried out in the context of a clinical trial and only in patients with good response before transplant.

VI. Plan and organizational structure of lesson – Appendix 1

VII. Materials for control and methodical providing lesson.

VII.1 control materials for a preparatory stage lesson.

Questions to control the output level of knowledge skills and abilities:

- Formulate a definition of HL, NHL, MM.

- Specify the key pathogenesis of HL, NHL, MM.
- Classifications of HL, NHL, MM.
- Main syndromes at HL, NHL, MM.
- Complications of HL, NHL, MM.
- Diagnostic criteria, differential diagnosis of HL, NHL, MM.
- Treatment of HL, NHL, MM.
- Supportive care of HL, NHL, MM.
- Prognosis and prophylaxis of HL, NHL, MM.

Tests for initial control:

1. What criteria are needed to take diagnosis Hodgkin lymphoma?
A. Increase of the lymph nodes
B. Violation of immunity
C. Hemorrhagic syndrome
D. *Presence Reed-Sternberg cells in the lymph nodes
E. Enlargement of liver and spleen
2. What from the next diseases is most probably related to high amount of plasma cells in the bone marrow?
A. Chronic myeloleukemia
B. Eritremiya
C. *Multiply myeloma
D. Chronic hepatitis
E. Acute leukemia
3. What from the next examination methods is the least informative in diagnostics of multiply myeloma?
A. Serum total protein level.
B. Serum beta2-microglobulin, albumin and globulin.
C. Radiography skeletal survey.
D. *Serum iron level
E. Complete blood count.
4. At a Hodgkin lymphoma in peripheral blood are observed:
A. Lymphocytosis
B. *Lymphopenia
C. Neutropenia
D. Basophilia
E. Reticulocytosis
5. The basic method of treatment of Hodgkin lymphoma of Ist stage is:
A. Radial therapy
B. Glucocorticoids
C. *Polychemotherapy
D. Leykophoresis
E. Blood transfusion
6. For a multiply myeloma are characteristic every clinical syndromes, except for:
A. *Ulcerative-necrotic
B. Anemic
C. Intoxicative
D. Hemorrhagic
E. Disproteinemic
7. What complaint is the most characteristic for patients with multiply myeloma?
A. General weakness
B. *Ostealgia
C. Dyspnea
D. Palpitation
E. Sweating.

VII.2 Materials of the methodical providing of the basic stage of lesson

Professional algorithm of curation of patient

(reference card) for forming of practical skills and abilities

№	Task	Sequence execution	Notes, warnings on self-control
1	*2*	*3*	*4*
1	To conduct the objective inspection of patient with HL, NHL, MM	1. To conduct collection of complaints, anamnesis of disease. 2. Carefully to collect anamnesis of life of patient. 3. To conduct a review patient. 4. To investigate the skin, lymphonodes. 5. To investigate the cardiovascular system of the patient (palpation, percussion).	Pay attention to the features, characteristics and conditions of pain syndrome and lymphadenopathy. Set risk factors and comorbidities lead to complications of main disease. Estimate the general state the patient, position in bed, color and moisture of the skin and mucous membranes. Estimate the size of lymphonodes, presence of hemorrhages. Pay attention to the rhythm of the pulse, presence pulse deficit, its tension and size on both hands, apical, its properties, limits of absolute and relative cardiac dullness, their changes in heart rate and BP
		6. Conduct heart auscultation and great vessels. 7. Conduct auscultation of the lungs. 8. To investigate the digestive system.	Pay attention to the incresed I tone, systolic murmurs. Set the presence of dyspnea, rales. Identify pain zones, hepatosplenomegaly.
2	To formulate a previous diagnosis.	1. Formulate and preliminary diagnosis. 2. Substantiate all components of previous diagnosis on the basis of complaints, medical history and life, physical examination	Based on the current classification formulate a preliminary diagnosis and substantiate every component.
3	To estimate the indexes of additional laboratory researches.	1. To estimate complete blood count. 2. To estimate urine tests. 3. To estimate proteinogram. 4. To estimate bone marrow slides.	Pay attention on the presence of anemia, leukocytosis or leukopenia, eosinophilia, lymphocytosis, high ESR. Pay attention to the presence of proteinuria. Pay attention to the presence of hyperproteinemia Pay attention to the lymphoid, myeloid or plasmocyte infiltration
4	To interpret information of additional instrumental researches.	1. To interpret chest, cerebral, abdominal X-ray, CT scan 2. To estimate lymphonode aspiration.	To pay attention to the presence on lymphadenopathy, pathology leads to bleeding, hepatosplenomegaly
5.	To conduct differential diagnostics.	1. Consistently find similarities in the complaints, medical history of the disease and life, objective status, data, laboratory and instrumental methods of examination of the patient and with similar nosology. 2. Find the differences between the complaints, according to medical history and life, objective symptoms, results of laboratory	Particular attention should be paid to the differential diagnosis of leukemia, renal failure, cancer, hemophilia, thrombocytopenia

		and instrumental methods of research and patient with similar nosology. 3. Based on the identified differences exclude similar disease from the list of possible diagnoses. 4. To the differential diagnosis by the aforementioned algorithm with all nosology that have similar clinical signs with the patient. 5. Given the impossibility to exclude anemia from a list of possible diagnoses draw a conclusion the greatest likelihood of such a diagnosis.	
6.	To formulate a final clinical diagnosis.	1. Formulate a final clinical diagnosis. 2. Based on the diagnosis, analysis of additional laboratory and instrumental methods conducted differential diagnosis to justify all the elements of the final clinical diagnosis.	Based on the current classification of lymphomas, multiply myeloma formulate previous diagnosis indicating the stage and severity of exacerbations, complications of the underlying disease and concomitant diseases.
7.	To administer treatment a patient.	1. Life style recommendations. 2. To administer drugs, other methods of treatment.	To indicate the regime and diet. Considering the age, the severity of disease, presence of complications and concomitant pathology appoint modern medical treatment according to the HL, NHL and MM guidelines.

VII.3 Materials of control for the final stage of lesson

Tests of III level (α=3).

Task №1

A patient, 60 years, complains of ostealgia, sweating, severe general weakness. Objectively: skin and mucus are pale. A liver is enlarged, it's border comes forward on 2 sm from under a costal arc. Blood test: Er.-3,5*10^{12}/l, Hb-90 g/l, CI-0,8; leuc-9,5x10^{9}/l, platelets -120*10^{9}/l, ESR - 70 mm/h. There are plasmatic cells. Total serum protein -115 g/l. In urine – Bens-Jones's protein. Chest X-ray: spontaneous fracture of IX rib, focal destruction in flat bones by sizes to 0,5 sm.

1) What is initial diagnosis?
2) What tests the patient needs to verify diagnosis?
3) What tactic of management?

Standard of answer:

1) Multiply myeloma.
2) Bone marrow aspiration, cytochemical and cytogenetic studies.
3) Polychemotherapy: melphalan/prednisone/thalidomide.

Task №2

Male, 24 years, complains of the conglomerate of not matted together compact, painless lymph nodes 4-5 sm in diameter in the right supraclavicular area, high temperature to 39 C^{o} periodically, skin itch and ostealgiae in pelvis and thorax. Blood count test: Hb-95 g/l, L-12*10^{9}/l, Eos. –10%, ESR -35 mm/hour. Chest X-ray: increase of mediastinal lymph nodes.

1) What is diagnosis?
2) What is plan of examination?
3) What tactic of management?

Standard of answer:
1) Hodgkin lymphoma, IIB stage.
2) Lymph node biopsy, bone marrow aspiration, cytochemical and cytogenetic studies.
3) Polychemotherapy: melphalan/prednisone/thalidomide.

VIII. Materials of the methodical providing of self-study of students: a reference card is for organization of independent work of students with educational literature

Task	Instructions
To learn etiology of HL, NHL, MM	List the basic etiologic factors of HL, NHL, MM
To learn pathogenesis of HL, NHL, MM	To select the key links of pathogenesis of HL, NHL, MM
To learn the clinical manifestation of HL, NHL, MM	To set symptoms and clinical syndromes which enable to offer the previous diagnosis of HL, NHL, MM
To learn the diagnostic criteria of HL, NHL, MM	To make the structural scheme of disease
To learn the investigation (laboratory, instrumental)	To make a plan of examination of patient with HL, NHL, MM
To learn specific changes of images and analyses at HL, NHL, MM	List the basic diagnostic criteria of HL, NHL, MM according to data of investigations
To conduct differential diagnostics, set a final clinical diagnosis	Substitute the basic components of diagnosis in accordance with modern classification, and to conduct a differential diagnosis
To administer the individual treatment patient with HL, NHL, MM	Wright down the list of prescriptions include the regime, diet, drug therapy considering the age, the severity of disease, presence of complications and concomitant pathology

THEME 29

HEMORRHAGIC CONDITIONS. HEMOPHILIA. THROMBOCYTOPENIC PURPURA.

Studying hours: 5 hours

I. Actuality of theme. Primary immune thrombocytopenia (ITP) is an acquired immune mediated disorder characterized by isolated thrombocytopenia, defined as a peripheral blood platelet count less than 100 x 10^9/L, and the absence of any underlying cause. Until recently, the abbreviation ITP stood for idiopathic thrombocytopenic purpura, but due to the current knowledge of the immune mediated mechanism of the disease, and the absence or minimal signs of bleeding in most cases have led to a revision of the terminology. In Europe, adult ITP has an incidence of 1.6 to 3.9 cases per 100,000 per year with increasing incidence with older age and equal for the sexes except in the mid-adult years (30-60 years), when the disease is more prevalent in women. Childhood ITP has an incidence of between 1.9 and 6.4 per 100,000 per year with equal distribution between the sexes.

Hemophilia A is an inherited, X-linked, recessive disorder caused by deficiency of functional plasma clotting factor VIII (FVIII). Significant rates of spontaneous mutation and acquired immunologic processes can result in this disorder as well. Hemophilia has an estimated frequency of approximately one in 10 000 births. Estimations based on the WFH's annual global surveys indicate that the number of people with hemophilia in the world is approximately 400 000. Hemophilia A is more common than hemophilia B, representing 80–85% of the total hemophilia population. Severe disease presents in children younger than 1 year and accounts for 43-70% of those with hemophilia A. Moderate disease presents in children aged 1-2 years and accounts for 15-26% of cases. Mild disease presents in children older than 2 years and accounts for 15-31% of cases.

II. Purposes of lesson.

- - ознайомити студентів із клінічними проявами геморагічних захворювань гемофілія (А, В та С) та тромбоцитопенія, диференціальним діагнозом, питаннями лікування і профілактики, реабілітації і експертизи втрати працездатності;
- навчити студентів проводити грамотне розпитування пацієнтів з деталізацією скарг, розпізнавати основні симптоми при геморагічних захворюваннях;
- ознайомити студентів з лабораторними методами дослідження необхідними для встановлення діагнозу гемофілії А, гемофілії В, гемофілії С та ІТП (ідіопатичної тромбоцитопенічної пурпури);
- навчити студентів самостійно трактувати результати коагулограм при гемофілії та тромбоцитопенії;
- навчити студентів правильно вибирати схему основного курсу лікування при гемофілії та тромбоцитопенії.
-
- History taking and physical examination of patients with LE, to reveal main symptoms and syndromes.

Student must know (α2):

- etiology and pathogenesis of hemophilia A, B and C and purpura;
- clinical signs of hemophilia and purpura.
- laboratory and image tests for diagnostics and differential diagnostics of hemophilia and purpura;
- principles and methods of treatment of hemophilia and purpura.

Students must acquire the skills (α 3):

- To take and substantiate diagnosis of hemophilia and purpura according to clinical data, laboratory and image tests;
- To take differential diagnostics and choose specific signs for every nosology (by algorithm);
- To write case history and list of prescriptions;
- To recognize with microscope blood and bone marrow samples in patients with thrombocytopenia.

To capture practical skills (α 3):

- To examine the patient with hemophilia and thrombocytopenia;
- To interpret complete blood test and coagulogram at hemophilia, thrombocytopenia and other hemorrhagic conditions;

- Management of patients with different hemorrhagic conditions;
- To reveal blood group.

III. Goals the development of personality (educational goals).

- The student must learn to follow the rules of conduct, principles of medical ethics and deontology bedside with hemophilia and thrombocytopenia;
- Possess the ability to establish psychological contact with the patient and his family;
- Acquires a sense of professional responsibility for the timeliness and adequacy of quality medical care.

IV. Interdisciplinary integration

1	*2*	*3*
1. Previous (providing)		
Normal anatomy	Vascular wall structure, it function	
Histology	Vascular wall structure, platelets	
Normal physiology	Physiology of vascular wall, platelets, clotting factors, fibrinolytic system. Main stages of hemostasis. Normative indices of laboratory and image tests, their value	To estimate laboratory and image tests in patient with hemorrhagic condition
Pathological physiology	Key links of pathogenesis of hemophilia and ITP	
Pathological anatomy	Morphological features of development of hemophilia and ITP	To analyze and interpret data of clinical inspection and investigation of patient
Pharmacology	Pharmacokinetics, pharmacodynamics, side effects of drugs used in the treatment of patients with hemophilia and ITP	Assign treatment, depending on age and individual characteristics of the patient, disease period. Define the optimal mode of reception and administration of drugs. Write recipes.
Propedeutics Internal Medicine	Basic stages and methods of clinical examination of the patient	Collect complaints, medical history, history of life, identify the main risk factors for anemia, conduct an objective examination of the patient's organs and systems, to identify the clinical features of hemophilia and ITP, interpret these additional laboratory and instrumental studies
2. Followings (provided)		
Emergency states	Risk factors and clinical manifestations of urgent conditions in patients with hemophilia and ITP: hemorrhage**s**	Render first aid in emergency conditions in patients with hemophilia and ITP: hemorrhage**s**
Hospital therapy	Clinical manifestation of complications and atypical forms of hemophilia and ITP, tactic of treatment	To determine the clinical displays of complications and atypical forms of a hemophilia and ITP, able to administer treatment
3. Interdisciplinary integration		
Rendu-Osler-Weber disease	Clinical manifestations of Rendu-Osler-Weber disease	Establish the characteristic clinical signs of Rendu-Osler-Weber disease and to perform differential diagnosis of hemophilia and ITP
Schönlein-Henoch disease	Clinical manifestations of Schönlein-Henoch disease	To determine the clinical signs of Schönlein-Henoch disease and to conduct differential diagnostics with hemophilia and ITP
Willebrand's disease	Clinical manifestations of Willebrand's disease	Establish the characteristic clinical signs of Willebrand's disease and to perform

		differential diagnosis of hemophilia and ITP

V. Contents of theme

Classification of hemorrhagic conditions, ICD-10.

Coagulation defects, purpura and other hemorrhagic conditions

- D65 Disseminated intravascular coagulation (defibrination syndrome)
- D66 Hereditary factor VIII deficiency
- D67 Hereditary factor IX deficiency
- D68 Other coagulation defects
- D69 Purpura and other hemorrhagic conditions
- D70-D77 Other disorders of blood and blood-forming organs
- D78-D78 Intraoperative and postprocedural complications of the spleen
- D80-D89 Certain disorders involving the immune mechanism

Immune thrombocytopenic purpura

Immune thrombocytopenia (ITP) is characterized by isolated thrombocytopenia often occurring in the absence of identifiable and specific precipitants. It is an autoimmune disorder characterized by immunologic destruction of otherwise normal platelets most commonly occurring in response to an unknown stimulus. ITP may occur in isolation (primary) or in association with other disorders (secondary). Secondary causes include autoimmune diseases, viral infections, and certain drugs:

- antiphospholipid syndrome;
- autoimmune thrombocytopenia (eg, Evans syndrome);
- common variable immune deficiency;
- drug administration side effect;
- infection with cytomegalovirus, helicobacter pylori, hepatitis C, human immunodeficiency virus, varicella zoster;
- lymphoproliferative disorders;
- bone marrow transplantation side effect;
- vaccination side effect;
- systemic lupus erythematosus.

*Primary ITP was defined by the International Working Group as a platelet count less than 100 *10^9/L in the absence of other causes or disorders that may be associated with thrombocytopenia.*

ITP is classified by duration into newly diagnosed, persistent (3-12 months' duration) and chronic (≥12 months' duration). Whereas ITP in adults typically has an insidious onset with no preceding viral or other illness and it normally follows a chronic course, ITP in children is usually short-lived with at least two-thirds recovering spontaneously within 6 months.

The annual incidence of ITP is estimated to be 5 cases per 100,000 children and 2 cases per 100,000 adults. Most cases of acute ITP, particularly in children, are mild and self-limited and may not receive medical attention. Therefore, estimated incidences of acute ITP are difficult to determine and are likely to understate the full extent of the disease. Children may be affected at any age with ITP, but the prevalence peaks in children aged 1-6 years. Adults may be affected at any age, but most cases are diagnosed in women aged 30-40 years. Onset in a patient older than 60 years is uncommon, and a search for other causes of thrombocytopenia is warranted. The most likely causes in these persons are myelodysplastic syndromes, acute leukemia, and marrow infiltration (myelophthisis). Persons with ITP who are 70 years or older are at increased risk for spontaneous bleeding and treatment-related adverse events. In children ITP is more common among boys compared with girls. In middle-aged adults, women are affected more frequently than men.

In persons with ITP, platelets are coated with autoantibodies to platelet membrane antigens, resulting in splenic sequestration and phagocytosis by mononuclear macrophages. The resulting shortened life span of platelets in the circulation, together with incomplete compensation by increased platelet production by bone marrow megakaryocytes, results in a decreased platelet count. In ITP, an abnormal autoantibody, usually immunoglobulin G (IgG) with specificity for 1 or more platelet membrane glycoproteins (GPs), binds to circulating platelet membranes. Autoantibody-coated platelets induce Fc receptor-mediated phagocytosis by mononuclear macrophages, primarily but not exclusively in the spleen. The spleen is the key organ in the

pathophysiology of ITP, not only because platelet autoantibodies are formed in the white pulp, but also because mononuclear macrophages in the red pulp destroy immunoglobulin-coated platelets. If bone marrow megakaryocytes cannot increase production and maintain a normal number of circulating platelets, thrombocytopenia and purpura develop. Impaired thrombopoiesis is attributed to failure of a compensatory increase in thrombopoietin and megakaryocyte apoptosis.

In children, most cases of ITP are acute, manifesting a few weeks after a viral illness. In adults, most cases of ITP are chronic, manifesting with an insidious onset, typically in middle-aged women. These clinical presentations suggest that the triggering events may be different. However, in both children and adults, the cause of thrombocytopenia (destruction of immunoglobulin-coated platelets by mononuclear macrophages) appears to be similar.

Autoantibody stimulation. In persons with chronic ITP, membrane GPs on the surface of platelets become immunogenic, stimulating the production of platelet autoantibodies. In persons with acute ITP, the stimulus for autoantibody production is also unknown. Platelet membrane cryptantigens may become exposed by the stress of infection, or pseudoantigens may be formed by the passive adsorption of pathogens on platelet surfaces.

Autoantibody specificity. In persons with chronic ITP, approximately 75% of autoantibodies are directed against platelet GPIIb/IIIa or GPIb/IX GP complexes. Presumably, the remaining 25% are directed against other membrane epitopes, including GPV, GPIa/IIa, or GPIV.

Role of the spleen. The spleen is the site of autoantibody production (white pulp). It is also the site of phagocytosis of autoantibody-coated platelets (red pulp). The slow passage of platelets through splenic sinusoids with a high local concentration of antibodies and Fc-gamma receptors on splenic macrophages lend to the uniqueness of the spleen as a site of platelet destruction. Low-affinity macrophage receptors, Fc gamma RIIA, and Fc gamma RIIIA bind immune-complexed IgG and are the key mediators of platelet clearance.

Platelet destruction. The mononuclear macrophage system of the spleen is responsible for removing platelets in ITP, because splenectomy results in prompt restoration of normal platelet counts in most patients with ITP. Platelets are sequestered and destroyed by mononuclear macrophages, which are neither reticular nor endothelial in origin. Therefore, the former designation of reticuloendothelial system is considered imprecise. Immune destruction of immunoglobulin-coated platelets is mediated by macrophage IgG Fc (Fc gamma RI, Fc gamma RII, and Fc gamma RIII) and complement receptors (CR1, CR3).

Signs and symptoms

Signs and symptoms vary widely. Many patients have either no symptoms or easy bruising (purpura) or extravasation of blood from capillaries into skin and mucous membranes (petechiae), whereas others experience serious bleeding, which may include gastrointestinal haemorrhage, extensive skin and mucosal haemorrhage, or intracranial haemorrhage.

Intracranial hemorrhage include the following:

- headache, blurred vision, somnolence, or loss of consciousness;
- hypertension and bradycardia, which may be signs of increased intracranial pressure;
- neurologic examination: any asymmetrical finding of recent onset.

The severity of thrombocytopenia correlates to some extent but not completely with the bleeding risk. Additional factors (e.g., age, lifestyle factors, uremia) affect the risk and should be evaluated before the appropriate management is determined. Although hemorrhagic death is a major concern it has been reported that the estimated rate of fatal hemorrhage is around 0.02 to 0.04 cases per adult patient-year risk.

Diagnosis of ITP is one of exclusion, when the history, physical examination, complete blood count and examination of peripheral blood smear do not suggest other etiology for the thrombocytopenia.

The ***medical history*** in a patient with a clinical suspicion of ITP should focus on factors that suggest another disease for which thrombocytopenia is a complication and signs and symptoms that differentiate mild, moderate, and severe bleeding tendencies.

Other systemic illnesses.

In adults, ITP may be a manifestation of systemic lupus erythematosus or acute or chronic leukemia. ITP may be a manifestation of a myelodysplastic syndrome, particularly in patients older than 60 years. In young children, ITP may manifest as a primary immune deficiency syndrome.

Postviral illness.

In children, most cases of ITP are acute, and onset seems to occur within a few weeks of recovery from a viral illness. The severity of symptoms of the viral illness is not correlated with the degree of thrombocytopenia. Thrombocytopenia is a recognized complication after infection with Epstein-Barr virus, varicella virus, cytomegalovirus, rubella virus, or hepatitis virus (A, B, or C), although the most typical association is a vaguely defined, viral, upper respiratory infection, or gastroenteritis. Transient thrombocytopenia has been reported to be associated with recent immunization with attenuated live-virus vaccines.

Human immunodeficiency virus (HIV) infection

Thrombocytopenia may occur during the acute retroviral syndrome coincident with fever, rash, and sore throat. ITP may be a manifestation of acquired immunodeficiency virus syndrome (AIDS), occurring late in the course of HIV infection. Thrombocytopenia not uncommonly marks the onset of symptomatic HIV infection, particularly in people who abuse drugs.

Helicobacter pylori infection

Studies from Italy and Japan indicate that many persons with ITP have H pylori gastric infections and that eradication of H pylori results in increased platelet counts. In the United States and Spain, the prevalence of H pylori infections does not appear to be increased in persons with ITP, and eradication of H pylori has not increased platelet counts. Therefore, routine testing for H pylori infections in adults and children with ITP is not recommended.

Drug-induced thrombocytopenia

Regard any medication taken by a person who develops thrombocytopenia as a potential causative agent. A history of all prescription and over-the-counter medications is required to exclude drug-related thrombocytopenia. More than 1444 currently approved drugs are listed in the US Food and Drug Administration's Adverse Event Reporting System database, all of which have been suspected of causing clinical episodes of thrombocytopenia. However, only 573 of these agents have a statistically significant reporting association with thrombocytopenia and of these, perhaps only two dozen satisfy clinical and laboratory criteria for evidence of causality for drug-induced thrombocytopenia. A medication suspected of causing thrombocytopenia should exhibit a strict temporal relationship with the development of the low platelet count; the platelet number should recover when the offending medication is discontinued; the likelihood of drug-induced thrombocytopenia should be greater than any other plausible cause; and ideally, in vitro evidence of drug-dependent antibody formation should exist. Reese et al have published a useful online database of the drugs most likely to cause thrombocytopenia. Persons who have been sensitized (by previous exposure) to quinidine or quinine may develop immune-mediated drug purpura within hours to days of subsequent exposure. To exclude drug purpura in a person previously treated with quinidine or quinine, the history must include questions about possible exposure to over-the-counter medications, tonic water in cocktails, or bitter lemon beverages. Investigate the records of patients who have been hospitalized and who develop acute thrombocytopenias for all of their medications that are listed and not listed in nursing charts. For example, people who are at risk for heparin-induced thrombocytopenia because of current or recent treatment with heparin may be receiving the heparin with the routine flushing of intravenous (IV) catheters, and this exposure may not be listed on the nursing medication sheet. Many catheters are also heparin impregnated, and unless checked, they can be a hidden cause of heparin-induced thrombocytopenia. Other drugs associated with drug purpura include antibiotics (eg, cephalosporins, rifampicin), gold salts, analgesics, neuroleptics, diuretics, antihypertensives, eptifibatide, and abciximab, which is a Fab fragment of the chimeric human-murine monoclonal antibody 7E3 directed against the platelet GPIIb/IIIa receptor.

Acute and chronic alcohol consumption may also be associated with thrombocytopenia. In persons with chronic liver disease, hypersplenism with secondary thrombocytopenia is not uncommon.

Bleeding tendency

Determine the extent and duration of the bleeding tendency to estimate the severity of the illness and the potential risk for a serious hemorrhage. Previous surgical history can often provide a useful clue regarding the acuteness of thrombocytopenia. Query patients to elicit signs or symptoms of intracranial bleeding, such as headache, blurred vision, somnolence, or loss of consciousness. Patients should report any recent accidental head trauma. Record any bleeding, including petechiae, ecchymoses, epistaxis, menorrhagia, melena, or hematuria. Determine if bruising or bleeding is a recurrent problem.

Physical examination

1. Findings that suggest another disease for which thrombocytopenia is a complication.
2. Physical signs that suggest serious internal bleeding.

ITP is a primary illness occurring in an otherwise healthy person. Signs of chronic disease, infection, wasting, or poor nutrition indicate that the patient has another illness.

- Vital signs: hypertension and bradycardia may be signs of increased intracranial pressure and evidence of an undiagnosed intracranial hemorrhage.
- Skin and mucous membranes:
  - widespread petechiae and ecchymoses, oozing from a venipuncture site, gingival bleeding, and hemorrhagic bullae indicate that the patient is at risk for a serious bleeding complication. If the patient's blood pressure was taken recently, petechiae may be observed under and distal to the area where the cuff was placed and inflated. Suction-type ECG leads may similarly induce petechiae.
  - mild thrombocytopenia and a relatively low risk for a serious bleeding complication may manifest as petechiae over the ankles in patients who are ambulatory or on the back in patients who are bedridden.
- Cardiovascular system: distant low-amplitude heart sounds accompanied by jugular venous distention may be evidence of hemopericardium.
- Abdomen:
  - in children with acute ITP, the presence of a readily palpable spleen is not typical.
  - in an adult, hepatosplenomegaly is also atypical for ITP and may indicate chronic liver and other diseases. In fact, splenomegaly excludes the diagnosis of ITP.
- Nervous system:
  - any asymmetrical finding of recent onset can indicate an intracranial hemorrhage;
  - pupils should be equal in size and have intact extraocular muscles and symmetrical eye movements;
  - balance and gait should be intact;
  - funduscopic examination reveals whether the margins of the optic disc are blurred. Examine the patient for the presence of retinal hemorrhages and other evidence of increased intracranial pressure.

Exams and tests

- Complete blood count: isolated thrombocytopenia (platelet count <100 x 10^9/L). Anemia (iron deficiency) only if due to significant bleeding -otherwise normal red cell indices, white blood cell count and differential.
- Peripheral blood smear: the morphology of RBCs and leukocytes is normal. The morphology of platelets is typically normal, with varying numbers of large platelets. Some persons with acute ITP may have megathrombocytes or stress platelets, reflecting the early release of megakaryocytic fragments into the circulation. If most of the platelets are large, approximating the diameter of RBCs, or if they lack granules or have an abnormal color, consider an inherited platelet disorder.
  Clumps of platelets on a peripheral smear prepared from ethylenediaminetetraacetic acid (EDTA)–anticoagulated blood are evidence of pseudothrombocytopenia. The diagnosis of this type of pseudothrombocytopenia is established if the platelet count is normal when repeated on a sample from heparin-anticoagulated or citrate-anticoagulated blood.
- Test for antibodies to HIV. In patients who have risk factors for HIV infection, a blood sample should be tested with an enzyme immunoassay for anti-HIV. During the acute HIV retroviral syndrome, the results of the anti-HIV assay may be negative. In this situation, a polymerase chain reaction for HIV DNA is more reliable than the anti-HIV assay.
- Test for antiplatelet antibodies. Assays for platelet antigen–specific antibodies, platelet-associated immunoglobulin, or other antiplatelet antibodies are available in some medical centers and certain mail-in reference laboratories. The reliability of the results of a platelet antibody test is highly specific to the laboratory used. A negative antiplatelet antibody assay result does not exclude the diagnosis of ITP. The authors do not recommend this test as part of the routine evaluation. Testing for antiplatelet antibodies is not required to diagnose ITP.

- Test for antinuclear antibodies (ANA). In selected women, the medical history may suggest a chronic, recurrent, multisystemic illness with vague, generalized signs or symptoms, such as recurrent, multiple, painful, tender, or swollen joints. In such cases, a negative ANA result is useful in diagnosing ITP if the patient's thrombocytopenia becomes chronic and resistant to treatment.
- Direct antiglobulin test: if anemia and thrombocytopenia are present, a positive direct antiglobulin (Coombs) test result may help establish a diagnosis of Evans syndrome.
- The detection of H pylori infection, preferably with the urea breath test or the stool antigen test, should be considered in the work-up of adults with typical ITP where it may have clinical impact20 (evidence level IIa). Serologic detection may be used but is less sensitive and less specific than the other tests; furthermore, the test may produce false positive results after IVIg therapy. Except in high-prevalence areas, the literature does not support routine testing in children with ITP.
- Bone marrow examination (aspirate and a biopsy) at baseline will be required for confirmation of diagnosis, especially in older population or those patients with non-typical presentation. In some situations bone marrow examination may also be required for other purpose; e.g. the use of TPO-R agonists has been associated with reports of an increase in bone marrow reticulin.

In adults who are thrombocytopenic and older than 60 years, we examine the bone marrow to exclude myelodysplastic syndrome or leukemia. In adults whose treatment includes corticosteroids, baseline pretreatment bone marrow aspiration may be useful for future reference. Many adults have treatment-resistant chronic ITP evident after 3-6 months of treatment, and an alternative diagnosis may be pursued vigorously at that time. Marrow aspirate obtained before any steroid-induced changes may have occurred can be useful. Perform bone marrow aspiration and biopsy to evaluate for possible hypoplasia or fibrosis before splenectomy is performed. In children, bone marrow examination is not required for the diagnosis of acute ITP, except in those with atypical hematologic findings, such as immature cells on the peripheral smear or persistent neutropenia. Many children with acute ITP have an increased number of normal or atypical lymphocytes on the peripheral smear, reflecting a recent viral illness. Unresponsiveness to standard treatment after 6 months is an indication for bone marrow aspiration.

Bone marrow aspirate. The cellularity of the aspirate and the morphology of erythroid and myeloid precursors should be normal. The number of megakaryocytes may be increased. Because the peripheral destruction of platelets is increased, megakaryocytes may be large and immature, although in many cases the megakaryocyte morphology is normal. Older patients require a careful examination of megakaryocyte morphology to exclude an early myelodysplastic syndrome.

Bone marrow biopsy. Sections of a needle biopsy specimen or marrow clot should reveal normal marrow cellularity, without evidence of hypoplasia or increased fibrosis.

Imaging Studies

- CT scanning and MRI are relatively benign and useful noninvasive imaging studies that can be used to rule out other causes of thrombocytopenia. However, they are not part of the routine evaluation of patients who may have ITP.
- Promptly perform CT scanning or MRI when the medical history or physical findings suggest serious internal bleeding.

Treatment

The goal of all treatment strategies for ITP is to achieve a platelet count that is associated with adequate hemostasis, rather than a normal platelet count. The management of ITP should be tailored to the individual patient and it is rarely indicated in those with platelet counts above 50 x 10^9/L in the absence of bleeding, trauma, surgery or high risk factors (e.g. patients on anticoagulation therapy).

The management of ITP varies widely.The majority of patients with no bleeding or mild bleeding (defined here as skin manifestations only, such as petechiae and bruising) can be treated with observation alone regardless of platelet count.

First-line treatment includes corticosteroids, intravenous immunoglobulin (IVIg) and anti-D immunoglobulin (anti-D) (the latter only for non-splenectomised Rh(D)positive patients).

Patients who fail to respond or who relapse face the options of treatment with second line drug therapy or splenectomy but there is no clear evidence to support the best approach. ***Splenectomy*** can provide long term efficacy in around 60% of cases. ***Second line drug therapies*** include high dose dexamethasone or methylprednisolone, high dose IV Ig or anti-D Ig, vinca alkaloids and danazol, the immunosuppressants

cyclophosphamide, azathioprine and cyclosporine or mycophenolate mofetil, and the anti CD-20 monoclonal antibody rituximab.

ITP is a disease of increased platelet destruction but recent evidence suggests that suboptimal platelet production by suppression of megakaryocyte function also occurs. Thrombopoietin receptor (TPO-R) agonists activate the thrombopoietin receptor (c-Mpl) which is the primary factor that regulates platelet production. Treatment aimed at increasing the platelet production has become a potential treatment option and TPO-R agonists have been approved in the EU as second line therapy for the treatment of chronic ITP.
Consider treatment for patients with a platelet count <30x10^9/L.
Longer courses of corticosteroids are preferred over shorter courses of corticosteroids or IVIg. IVIg may be used in conjunction with corticosteroids if a more rapid increase in platelet count is required. Either IVIg (1g/kg for one dose, repeated as necessary) or anti-D (in appropriate patients) may be used as a first-line treatment if corticosteroids are contraindicated.
Adults who have a platelet count >30x10^9/L and are asymptomatic following splenectomy do not require further therapy.
The IWG provides specific recommendations for assessing the response to ITP treatments (Table 8).

Table 8. **Definitions of response to treatment by ITP**.

Complete response (CR)	A platelet count ≥100*10^9/L measured on 2 occasions >7 days apart and the absence of bleeding
Response (R)	A platelet count ≥30 *10^9/L and a greater than 2-fold increase in platelet count from baseline measured on 2 occasions >7 days apart and the absence of bleeding
No response (NR)	A platelet count <30 *10^9/L or a less than 2-fold increase in platelet count from baseline measu or the presence of bleeding. Platelet count must be measured on 2 occasions more than a day apart red on 2 occasions >7 days apart

Table 9. **Special considerations for patients with ITP**

Splenectomy	Recommended for adults who have failed corticosteroid therapy, with similar efficacy with open or laparoscopic procedures
Rituximab	May be considered for adults at risk of bleeding who have failed one line of therapy such as corticosteroids, IVIg, or splenectomy
Thrombopoietin receptor agonists	Recommended for adults at risk of bleeding who relapse after splenectomy or who have a contraindication to splenectomy and who have failed at least one other therapy. These agents may also be considered for adults at risk of bleeding who have failed one line of therapy such as corticosteroids or IVIg and who have not undergone splenectomy.
High-dose dexamethasone	May be considered for children or adolescents with ITP who have significant ongoing bleeding and/or have a need for improved quality of life despite conventional treatment
Immunosuppression	Multiple agents have been reported; however data for any one specific agent remain insufficient for specific recommendations

Given the goals and considerations mentioned above, treatment of acute ITP requires considerable individualization. Adults whose disease is not controlled with a prednisone-induced increase in platelet count that is maintained by IV RhIG or IVIG and whose conditions do not respond to 4 weekly infusions of rituximab are candidates for splenectomy. After these serial experiences, such patients are likely to have had thrombocytopenia for at least 6 months and, therefore, are categorized as having chronic ITP. Eltrombopag or romiplostim offer potential maintenance of safe levels of platelet counts for adults who qualify by having ITP for at least 6 months and whose conditions are refractory to conventional medical management

(prednisone, IV RhIG, IVIG, rituximab), and whose platelet count is not maintained in a satisfactory range after splenectomy.

The treatment of chronic, refractory ITP may introduce risks of toxicity from medications that are comparable in severity to the risks of untreated thrombocytopenia. These treatments also may impact adversely on the patient's quality of life. For patients with chronic refractory ITP who have access to investigational programs, the authors encourage them to participate in controlled clinical trials to support the development of effective treatments for this category.

Secondary ITP (HIV- associated)

- Treatment of the underlying HIV infection with antiviral therapy should be considered prior to other treatment options unless the patient has clinically significant bleeding.
- IVIg, corticosteroids, or anti-D may be used initially for patients requiring further therapy.
- Splenectomy is considered preferable to other agents in symptomatic patients who have failed initial drug therapy.

Secondary ITP (HCV- associated)

- Antiviral therapy should be considered in the absence of contraindications, but the platelet count should be closely monitored in these situations due to a risk of worsening thrombocytopenia attributable to interferon.
- If treatment is required, the initial management shouldbe with IVIg.

Secondary ITP (H. pylori- associated)

- Routine testing for H.pylori is not recommended in asymptomatic children with unresolved ITP.
- Screening for H.pylori should be considered in adults for whom eradication therapy would be undertaken if testing were positive.
- Eradication therapy for H.pylori should be administered to patients who are found to have infection

ITP in Pregnancy:

- Pregnant patients requiring treatment should receive either corticosteroids or IVIg.
- For pregnant women with ITP, the mode of delivery should be based on obstetric indications.

Medication Summary

Corticosteroids. Corticosteroids are the treatment of choice for initial management of acute ITP. Increase the platelet count by decreasing splenic uptake of autoantibody-coated platelets and by decreasing synthesis of autoantibody. Dosages must be tapered after a safe platelet count is achieved, and the drug is replaced with IV RhIG or IVIG to avoid serious complications of chronic hypercorticism.

Prednisolone. Oral corticosteroid that is used most frequently because of its relatively low cost, known adverse effects, and long-term clinical record. Drugs of choice (DOC) for initial treatment of ITP in children and adults. For aggressive treatment, may be combined with IV RhIG or IVIG. In emergency, replace PO prednisone with IV methylprednisolone.

Methylprednisolone. DOC for the initial management of severe bleeding tendency in ITP. IV is recommended when the most rapid and reliable treatment of ITP is required. In this situation, combine with IV RhIG in qualified Rh(D)-positive patients or IVIG in Rh(D)-negative patients or unqualified Rh(D)-positive patients.

Blood Products. Blood products are used to improve clinical and immunologic aspects of ITP. These products may decrease autoantibody production and increase solubilization and removal of immune complexes.

IV RhIG (WinRho SDF). Specialized immunoglobulin product manufactured from pools of plasma from Rh(D)-negative persons and alloimmunized to D blood group antigen. Subjected to anion-exchange column chromatography to permit IV infusion and solvent-detergent treatment and nanofiltration to reduce infectivity by lipid-enveloped viruses. Induces immune RBC hemolysis in Rh(D)-positive recipients, decreasing function of mononuclear macrophages (reticuloendothelial blockade) and sparing immunoglobulin-coated platelets from splenic destruction.

IVIG (Gamimune, Sandoglobulin). Large dose of 1 g/kg induces decreased function of mononuclear macrophages (reticuloendothelial blockade), sparing immunoglobulin-coated platelets from splenic destruction. Used with IV methylprednisolone to manage acute ITP in children. Decreased time to an increased platelet count compared with IV RhIG, but the difference does not appear to be clinically significant. Compared with IV RhIG, associated with more adverse effects, longer infusions, and increased

cost, causing many hematologists to prefer IV RhIG as a supplement to corticosteroids, at least for Rh(D)-positive patients.

Immunosuppressive Antimetabolites. Immunosuppressive antimetabolites are used in patients ITP to reduce production of abnormal autoantibodies.

Azathioprine (Imuran). May be effective in some patients with ITP whose conditions do not or no longer have response to corticosteroids, IV RhIG, or IVIG. May be used with prednisone to reduce dose of prednisone or as another PO medication to delay splenectomy.

Synthetic Antineoplastic Drugs. Synthetic antineoplastic drugs are chemically related to nitrogen mustards. These agents inhibit cell growth and proliferation.

*Cyclophosphamide (Cytoxan).*May be useful in some patients whose conditions do not or no longer have a response to corticosteroids, IV RhIG, IVIG, or splenectomy. Induces less of a decrease in platelet count than other immunosuppressive alkylating agents.

Androgens. The steroidogenic properties of androgens may modulate the immune system.

*Danazol (Danocrine).*May impair the clearance of immunoglobulin-coated platelets and decreases autoantibody production. Increased platelet counts in 40-50% of patients, particularly postmenopausal women.

Monoclonal Antibodies. Monoclonal antibodies are chimeric murine-human monoclonal antibodies directed against CD20 on B lymphocytes.

Rituximab (Rituxan). Chimeric monoclonal antibody directed against the CD20 antigen on the surface of normal and malignant B lymphocytes. Antibody is IgG kappa immunoglobulin with murine light- and heavy-chain variable sequences and human constant region sequences.

Thrombopoietin-Receptor Agonists. These new agents directly stimulates bone marrow platelet production.

Romiplostim (Nplate). An Fc-peptide fusion protein (peptibody) that increases platelet production through binding and activation of the thrombopoietin (TPO) receptor, a mechanism similar to endogenous TPO. Indicated for chronic immune (idiopathic) thrombocytopenic purpura in patients who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Eltrombopag (Promacta) Oral TPO receptor agonist. Interacts with transmembrane domain of human TPO receptor and induces megakaryocyte proliferation and differentiation from bone marrow progenitor cells. Indicated for thrombocytopenia associated with chronic idiopathic thrombocytopenic purpura in patients experiencing inadequate response to corticosteroids, immunoglobulins, or splenectomy. Not for use to normalize platelet counts, but used when clinical condition increases bleeding risk.

HEMOPHILIA

Hemophilia is an X-linked congenital bleeding disorder caused by a deficiency of coagulation factor VIII (FVIII) (in hemophilia A) or factor IX (FIX) (in hemophilia B). The deficiency is the result of mutations of the respective clotting factor genes. Hemophilia has an estimated frequency of approximately one in 10 000 births. Estimations based on the WFH's annual global surveys indicate that the number of people with hemophilia in the world is approximately 400 000. 4. Hemophilia A is more common than hemophilia B, representing 80–85% of the total hemophilia population. Hemophilia generally affects males on the maternal side. However, both F8 and F9 genes are prone to new mutations, and as many as 1/3 of all cases are the result of spontaneous mutation where there is no prior family history.

Hemophilia is one of the oldest described genetic diseases. An inherited bleeding disorder in males was recognized in Talmudic records of the second century. The modern history of hemophilia began in 1803 with the description of hemophilic kindred by John Otto, followed by the first review of hemophilia by Nasse in 1820. Wright demonstrated evidence of laboratory defects in blood clotting in 1893; however, FVIII was not identified until 1937 when Patek and Taylor isolated a clotting factor from the blood, which they called antihemophilia factor (AHF). A bioassay of FVIII was introduced in 1950. Although the intimate relationship between FVIII and von Willebrand factor (vWF) is now known, it was not appreciated at the time. In 1953, decreased factor FVIII in patients with vWF deficiency was first described. Further research by Nilson and coworkers indicated the interaction between these 2 clotting factors. In 1952, Christmas disease was described and named after the surname of the first patient who was examined in detail. This disease was distinct from hemophilia because mixing plasma from a patient with "true hemophilia" and with plasma from a patient with Christmas disease corrected the clotting time; thus, hemophilia A and B were differentiated. Hemophilia A makes up approximately 80% of hemophilia cases. In the early 1960s, cryoprecipitate was the first concentrate available for the treatment of patients with hemophilia. In the

1970s, lyophilized intermediate-purity concentrates were obtained from a large pool of blood donors. The introduction of concentrated lyophilized products that are easy to store and transport has dramatically improved the quality of life of patients with hemophilia and facilitated their preparation for surgery and home care. Unfortunately, the large size of the donor pool—as many as 20,000 donors may contribute to a single lot of plasma-derived FVIII concentrate—heightened the risk of viral contamination of commercial FVIII concentrates. By the mid 1980s, most patients with severe hemophilia had been exposed to hepatitis A, hepatitis B, and hepatitis C viruses and human immunodeficiency virus (HIV). Viricidal treatment of plasma-derived FVIII concentrates have been effective in eliminating new HIV transmissions and virtually eliminating hepatitis B and hepatitis C exposures. The introduction of recombinant FVIII concentrate, and the gradual elimination of albumin from the production process used for these products, has virtually eliminated the risk of viral exposure.

Pathophysiology. Factor VIII deficiency, dysfunctional factor VIII, or factor VIII inhibitors lead to the disruption of the normal intrinsic coagulation cascade, resulting in spontaneous hemorrhage and/or excessive hemorrhage in response to trauma. Hemorrhage sites include joints (eg, knee, elbow), muscles, CNS, GI system, genitourinary system, pulmonary system, and cardiovascular system. Intracranial hemorrhage is most common in patients younger than 18 years and can be fatal.

The clotting cascade.

The role of the coagulation system is to produce a stable fibrin clot at sites of injury. The clotting mechanism has 2 pathways: intrinsic and extrinsic. The intrinsic system is initiated when factor XII is activated by contact with damaged endothelium. The activation of factor XII can also initiate the extrinsic pathway, fibrinolysis, kinin generation, and complement activation. In conjunction with high-molecular-weight kininogen (HMWK), factor XIIa converts prekallikrein (PK) to kallikrein and activates factor XI. Activated factor XI, in turn, activates factor IX in a calcium-dependent reaction. Factor IXa can bind phospholipids. Then, factor X is activated on the cell surface; activation of factor X involves a complex (tenase complex) of factor IXa, thrombin-activated FVIII, calcium ions, and phospholipid. In the extrinsic system, the conversion of factor X to factor Xa involves tissue factor (TF), or thromboplastin; factor VII; and calcium ions. TF is released from the damaged cells. It is thought to be a lipoprotein complex that acts as a cell surface receptor for FVII, with its resultant activation. It also adsorbs factor X to enhance the reaction between factor VIIa, factor X, and calcium ions. Factor IXa and factor XII fragments can also activate factor VII. In the common pathway, factor Xa (generated through the intrinsic or extrinsic pathways) forms a prothrombinase complex with phospholipids, calcium ions, and thrombin-activated factor Va. The complex cleaves prothrombin into thrombin and prothrombin fragments 1 and 2. Thrombin converts fibrinogen into fibrin and activates FVIII, factor V, and factor XIII. Fibrinopeptides A and B, the results of the cleavage of peptides A and B by thrombin, cause fibrin monomers to form and then polymerize into a meshwork of fibrin; the resultant clot is stabilized by factor XIIIa and the cross-linking of adjacent fibrin strands. Because of the complex interactions of the intrinsic and extrinsic pathways (factor IXa activates factor VII), the existence of only one in vivo pathway with different mechanisms of activation has been suggested. FVIII and FIX circulate in an inactive form. When activated, these 2 factors cooperate to cleave and activate factor X, a key enzyme that controls the conversion of fibrinogen to fibrin. Therefore, the lack of FVIII may significantly alter clot formation and, as a consequence, result in clinical bleeding.

The gene for FVIII (ie, hemophilia A) is located on the long arm of chromosome X, within the Xq28 region. The gene (F8C) is unusually large, representing 186 kb of the X chromosome. It comprises 26 exons and 25 introns. Mature FVIII contains 2332 amino acids. Approximately 40% of cases of severe FVIII deficiency arise from a large inversion that disrupts the FVIII gene. Deletions, insertions, and point mutations account for the remaining 50-60% of hemophilia A defects. Low FVIII levels may arise from defects outside the FVIII gene, as in type IIN von Willebrand disease, in which the molecular defect resides in the FVIII-binding domain of von Willebrand factor.

Hemophilia A is caused by an inherited or acquired genetic mutation or an acquired factor VIII inhibitor. The defect results in the insufficient generation of thrombin by the FIXa and FVIIIa complex by means of the intrinsic pathway of the coagulation cascade. This mechanism, in combination with the effect of the tissue-factor pathway inhibitor, creates an extraordinary tendency for spontaneous bleeding.

This disorder is inherited in an X-linked recessive pattern. The gene for FVIII is located on the long arm of the X chromosome in band q28. The factor VIII gene is one of the largest genes; it is 186 kilobases

(kb) long and has a 9-kb coding region that contains 26 exons. The mature protein contains 2332 amino acids and has a molecular weight of 300 kd. It includes 3 A domains, 1 B domain, and 2 C domains.

Numerous mutations in the gene structure have been described. Genetic abnormalities include genetic deletions of variable size, abnormalities with stop codons, and frame-shift defects. Data suggest that 45% of severe hemophilia A cases result from an inversion mutation.

Because hemophilia is an X-linked, recessive condition, it occurs predominantly in males. Females usually are asymptomatic carriers. However, mild hemophilia may be more common in carriers than previously recognized. In 1 study, 5 of 55 patients with mild hemophilia (factor levels 5-50%) were girls. Females may have clinical bleeding due to hemophilia if 1 of 3 conditions is present: extreme lyonization (ie, inactivation of the normal FVIII allele in one of the X chromosomes), homozygosity for the hemophilia gene (ie, father with hemophilia and mother who is a carrier, two independent mutations, or some combination of inheritance and new mutations), or Turner syndrome (XO) associated with the affected hemophilia gene. Significant deficiency in FVIII may be evident in the neonatal period. It continues through the life of the affected individual. The absence of hemorrhagic manifestations at birth does not exclude hemophilia.

Clinical manifestation

Signs of hemorrhage include the following:

- General - weakness and orthostasis.
- Musculoskeletal (joints) - tingling, cracking, warmth, pain, stiffness, and refusal to use joint (children).
- CNS - headache, stiff neck, vomiting, lethargy, irritability, and spinal cord syndromes.
- GI - hematemesis, melena, frank red blood per rectum, and abdominal pain.
- Genitourinary - hematuria, renal colic, and post circumcision bleeding.
- Other - epistaxis, oral mucosal hemorrhage, hemoptysis, dyspnea (hematoma leading to airway obstruction), compartment syndrome symptoms, and contusions; excessive bleeding with routine dental procedures.

Signs of infectious disease include the following:

- HIV/AIDS-related symptoms.
- Hepatitis-related symptoms.

The hallmark of hemophilia is hemorrhage into the joints. This bleeding is painful and leads to long-term inflammation and deterioration of the joint, resulting in permanent deformities, misalignment, loss of mobility, and extremities of unequal lengths. Human synovial cells synthesize high levels of tissue factor pathway inhibitor, resulting in a higher degree of factor Xa (FXa) inhibition, which predisposes hemophilic joints to bleed. This effect may also account for the dramatic response of FVIIa infusions in patients with acute hemarthroses and FVIII inhibitors. Synovial hypertrophy, hemosiderin deposition, fibrosis, and damage to cartilage progress, with subchondral bone-cyst formation. Bleeding into a joint may lead to synovial inflammation, which predisposes the joint to further bleeds. A joint that has had repeated bleeds (by one definition, at least 4 bleeds within a 6-month period) is termed a target joint. Commonly, this occurs in knees.

Male patients with severe hemophilia present at circumcision. Easy bruising may occur at the start of ambulation or primary dentition. The patient may have a history of hemarthroses and prolonged bleeding with surgical procedures, trauma, dental extraction, and he or she may have spontaneous bleeding in soft tissues. A traumatic challenge relatively late in life may have to occur before mild or moderate hemophilia is diagnosed. Factors that elevate factor VIII (FVIII) levels (eg, age, ABO blood type, stress, exercise) may mask mild hemophilia. The principal sites of bleeding in patients with hemophilia are as follows. Bleeds affect weight-bearing joints and other joints. The muscles most commonly affected are the flexor groups of the arms and gastrocnemius of the legs. Iliopsoas bleeding is dangerous because of the large volumes of blood loss and because of compression of the femoral nerve. In the genitourinary tract, gross hematuria may occur in as many as 90% of patients. In the GI tract, bleeding may complicate common GI disorders. Bleeding in the CNS is the leading cause of hemorrhagic death among patients with hemophilia.

Physical Examination

Signs of hemorrhage include the following:

- tachycardia;
- tachypnea;
- hypotension;
- orthostasis.

Organ system–specific signs of hemorrhage include the following:

- Musculoskeletal (joints) - tenderness, pain with movement, decreased range of motion, effusion, and warmth.
- CNS - abnormal neurologic exam findings, altered mental status, and meningismus.
- GI - can be painless; hepatic/splenic tenderness, and peritoneal signs.
- Genitourinary - bladder spasm/distension/pain and costovertebral angle pain.
- Other - hematoma leading to location-specific signs (eg, airway obstruction, compartment syndrome).

Approximately 30-50% of patients with severe hemophilia present with manifestations of neonatal bleeding (eg, after circumcision). Approximately 1-2% of neonates have intracranial hemorrhage. Other neonates may present with severe hematoma and prolonged bleeding from the cord or umbilical area.

After the immediate neonatal period, bleeding is uncommon in infants until they become toddlers, when trauma-related soft-tissue hemorrhage occurs. Young children may also have oral bleeding when their teeth are erupting. Bleeding from gum and tongue lacerations is often troublesome because the oozing of blood may continue for a long time despite local measures. As physical activity increases in children, hemarthrosis and hematomas occur. Chronic arthropathy is a late complication of recurrent hemarthrosis in a target joint. Traumatic intracranial hemorrhage is a serious life-threatening complication that requires urgent diagnosis and intervention. Petechiae usually do not occur in patients with hemophilia because they are manifestations of capillary blood leaking, which is typically the result of vasculitis or abnormalities in the number or function of platelets. Hemophilia is classified according to the clinical severity as mild, moderate, or severe (see Table 1, below). Patients with severe disease usually have less than 1% factor activity. It is characterized by spontaneous hemarthrosis and soft tissue bleeding in the absence of precipitating trauma. Patients with moderate disease have 1-5% factor activity and bleed with minimal trauma. Patients with mild hemophilia have more than 5% factor VIII (FVIII) activity and bleed only after significant trauma or surgery.

The ***classification*** of the severity of hemophilia has been based on either clinical bleeding symptoms or on plasma procoagulant levels; the latter are the most widely used criteria. Persons with less than 1% normal factor (< 0.01 IU/mL) are considered to have severe hemophilia. Persons with 1-5% normal factor (0.01-0.05 IU/mL) are considered to have moderately severe hemophilia. Persons with more than 5% but less than 40% normal factor (>0.05 to < 0.40 IU/mL) are considered to have mild hemophilia.

Clinical bleeding symptom criteria have been used because patients with FVIII levels of less than 1% occasionally have little or no spontaneous bleeding and appear to have clinically moderate or mild hemophilia. Furthermore, the reverse is true for patients with procoagulant activities of 1-5%, who may present with symptoms of clinically severe disease. The severity of bleeding in hemophilia is generally correlated with the clotting factor level, as shown in Table 10.

Table 10. **Relationship of bleeding severity with clotting factor level**

Severity	Clotting factor level	Bleeding episodes
Severe	<1 IU dL^{-1} (<0.01 IU mL^{-1}) or <1% of normal	Spontaneous bleeding into joints or muscles, predominantly in the absence of identifiable hemostatic challenge
Moderate	1–5 IU dL^{-1} (0.01–0.05 IU mL^{-1}) or 1–5% of normal	Occasional spontaneous bleeding; prolonged bleeding with minor trauma or surgery
Mild	5–40 IU dL^{-1} (0.05–0.40 IU mL^{-1}) or 5 to <40% of normal	Severe bleeding with major trauma or surgery. Spontaneous bleeding is rare

Laboratory studies

- Complete blood cell count.
- Coagulation studies.
- A factor VIII assay.

On the hemoglobin/hematocrit, expect normal or low values. Expect a normal platelet count. On coagulation studies, the bleeding time and prothrombin time (which assesses the extrinsic coagulation pathway) are normal.
Usually, the activated partial thromboplastin time (aPTT) is prolonged; however, a normal aPTT does not exclude mild or even moderate hemophilia because of the relative insensitivity of the test. The aPTT is significantly prolonged in severe hemophilia.
For FVIII assays, levels are compared with a normal pooled-plasma standard, which is designated as having 100% activity or the equivalent of FVIII U/mL. Normal values are 50-150%. Values in hemophilia are as follows:

- Mild: >5%
- Moderate: 1-5%
- Severe: < 1%

Spontaneous bleeding complications are severe in individuals with undetectable activity (< 0.01 U/mL), moderate in individuals with activity (2-5% normal), and mild in individuals with factor levels greater than 5%.
Differentiation of hemophilia A from von Willebrand disease is possible by observing normal or elevated levels of von Willebrand factor antigen and ristocetin cofactor activity. Bleeding time is prolonged in patients with von Willebrand disease but normal in patients with hemophilia.
In patients with an established diagnosis of hemophilia, periodic laboratory evaluations include screening for the presence of FVIII inhibitor and screening for transfusion-related or transmissible diseases such as hepatitis and HIV infection. Screening for infection may be less important in patients who receive only recombinant FVIII concentrate.

Testing for inhibitors

Laboratory confirmation of a FVIII inhibitor is clinically important when bleeding is not controlled after adequate amounts of factor concentrate are infused during a bleeding episode. For the assay, the aPTT measurement is repeated after incubating the patient's plasma with normal plasma at 37°C for 1-2 hours. If the prolonged aPTT is not corrected, the inhibitor concentration is titrated using the Bethesda method. By convention, more than 0.6 Bethesda units (BU) is considered a positive result for an inhibitor. Less than 5 BU is considered a low titer of inhibitor, and more than 10 BU is a high titer. The distinction is clinically significant, as patients with low-titer inhibitors may respond to higher doses of FVIII concentrate.

Imaging studies for acute bleeds

Early and aggressive imaging is indicated, even with low suspicion for hemorrhage, after coagulation therapy is initiated. Imaging choices are guided by clinical suspicion and anatomic location of involvement. Head CT scans without contrast are used to assess for spontaneous or traumatic intracranial hemorrhage. Perform magnetic resonance imaging on the head and spinal column for further assessment of spontaneous or traumatic hemorrhage. MRI is also useful in the evaluation of the cartilage, synovium, and joint space.
Ultrasonography is useful in the evaluation of joints affected by acute or chronic effusions. This technique is not helpful for evaluating the bone or cartilage. Special studies such as angiography and nucleotide bleeding scan may be clinically indicated.

Radiography for joint assessment is of limited value in acute hemarthrosis. Evidence of chronic degenerative joint disease may be visible on radiographs in patients who are untreated or inadequately treated or in those with recurrent joint hemorrhages. In these patients, radiographs may show synovial hypertrophy, hemosiderin deposition, fibrosis, and damage to cartilage that progresses with subchondral bone cyst formation. Hemophilic arthropathy evolves through 5 stages, starting as an intra-articular and periarticular edema due to acute hemorrhage and progressing to advanced erosion of the cartilage with loss of the joint space, joint fusion, and fibrosis of the joint capsules.

Treatment

The treatment of hemophilia may involve management of hemostasis, management of bleeding episodes, use of factor replacement products and medications, treatment of patients with factor inhibitors, and treatment and rehabilitation of patients with hemophilia synovitis.

Ambulatory replacement therapy for bleeding episodes is essential for preventing chronic arthropathy and deformities. Home treatment and infusion by the family or patient is possible in most cases.

Prompt and appropriate treatment of hemorrhage is important to prevent long-term complications and disability.

Dose calculations are directed toward achieving a factor VIII (FVIII) activity level of 30-40% for most mild hemorrhages, of at least 50% for severe bleeds (eg, from trauma) or prophylaxis of major dental surgery or major surgery, and 80-100% in life-threatening hemorrhage. Hospitalization is reserved for severe or life-threatening bleeds, such as large-soft tissue bleeds; retroperitoneal hemorrhage; and hemorrhage related to head injury, surgery, or dental work.

Patients are treated with prophylaxis or intermittent, on-demand therapy for bleeding events. Prophylaxis has been shown in many studies to prevent or at least reduce the progression of damage to target sites, such as joints. According to a review of 6 randomized controlled trials, preventative therapy started early in childhood, as compared to on-demand treatment, is able to reduce total bleeds and bleeding into joints resulting in a decrease in overall joint deterioration and an improvement in patient quality of life.

In most developed countries with access to recombinant product, prophylaxis is primary (ie, therapy is started in patients as young as 1 y and continues into adolescence). A cost-benefit analysis indicates that this approach reduces overall factor use and significantly reduces morbidity. In situations in which this is not feasible, secondary prophylaxis (ie, therapy after a target joint has developed, to prevent worsening of the joint) is instituted for a defined period.

Dosing is designed to maintain trough levels greater than 2%. This usually requires the administration of FVIII 3 times per week. Individualized therapy (ie, tailored prophylaxis) has been also used with success; the best approach has yet to be determined.

Hospitalizing patients with internal bleeding, with uncontrollable bleeding, and before elective surgery or other invasive procedures is advised.

Emergency department care.

Before a patient with hemophilia is treated, the following information should be obtained:

- The type and severity of factor deficiency
- The nature of the hemorrhage or the planned procedure
- The patient's previous treatments with blood products
- Whether inhibitors are present and if so, their probable titer
- Any previous history of desmopressin acetate (DDAVP) use (mild hemophilia A only), with the degree of response and clinical outcome.

Use aggressive hemostatic techniques. Correct coagulopathy immediately. Include a diagnostic workup for hemorrhage, but never delay indicated coagulation correction pending diagnostic testing. If possible, draw blood for the coagulation studies, including 2 blue-top tubes to be spun and frozen for factor and inhibitor assays.

Patients whose condition and bleeding are stabilized should be transferred to a specialized center for further treatment and monitoring because a multidisciplinary approach by specialists experienced in hemophilia may be required.

Further outpatient care for patients with minor hemorrhage (not life threatening) consists of continued hemostatic measures (eg, brief joint immobilization, bandage). Hematologist or primary care physician follow-up care is indicated. The patient should continue factor replacement and monitoring.

If a patient has HIV seroconversion, arrange appropriate outpatient care at a specialty infectious disease clinic, monitor the patient's CD4 count, observe the patient for adverse effects of anti-HIV treatment, and monitor for and treat possible opportunistic infections.

Factor VIII concentrates

Various FVIII concentrates are now available to treat hemophilia A. Fresh frozen plasma and cryoprecipitate are no longer used in hemophilia because of the lack of safe viral elimination and concerns regarding volume overload. Various purification techniques are used in plasma-based FVIII concentrates to reduce or eliminate the risk of viral transmission, including heat treatment, cryoprecipitation, and chemical precipitation. These techniques inactivate viruses such as hepatitis B virus, hepatitis C virus, and HIV. However, the transmission of nonenveloped viruses (eg, parvovirus and hepatitis A virus) and poorly characterized agents (eg, prions) is still a potential problem. Many recombinant FVIII concentrates are now available. The advantage of such products is the elimination of viral contamination. Third-generation products without any exposure to animal proteins are now available to further decrease this risk. The effectiveness of these products appears comparable to that of plasma-derived concentrates. Concerns

regarding higher incidences of the presence of inhibitor appear to be unwarranted. With wider availability of improved products (ie, better stability, purity), use of continuous infusion of factors has incrementally increased. Continuous administration of antihemophilic factors prevents the peaks and valleys in factor concentrations that occur with intermittent infusion; this benefit is particularly important when treatment is required for prolonged periods. Besides improved hemostasis, continuous infusions decreases the amount of factor used, which can result in significant savings. The indications for this approach include intracranial hemorrhage, vascular compromise, iliopsoas bleeding, and preparation for surgery. In most minor-to-moderate bleeding episodes, intermittent boluses are adequate. Intermittent boluses can also be used prophylactically, especially in the treatment of recurrent bleeding in target joints.

Doses of FVIII concentrate are calculated according to the severity and location of bleeding (table 11, 12). As a rule, FVIII 1 U/kg increases FVIII plasma levels by 2%. The reaction half-time is 8-12 hours. Target levels by hemorrhage severity are as follows:

- Mild hemorrhages (ie, early hemarthrosis, epistaxis, gingival bleeding): Maintain an FVIII level of 30%
- Major hemorrhages (ie, hemarthrosis or muscle bleeds with pain and swelling, prophylaxis after head trauma with negative findings on examination): Maintain an FVIII level of 50%
- Life-threatening bleeding episodes (ie, major trauma or surgery, advanced or recurrent hemarthrosis): Maintain an FVIII level of 80-90%. Plasma levels are maintained above 40-50% for a minimum of 7-10 days.

One unit of factor VIII is the amount of factor VIII in 1 mL of plasma (1 U/mL or 1%). The volume of distribution of factor VIII is that of plasma, approximately 50 mL/kg. The difference between the desired factor VIII activity level and the patient's native factor VIII activity level can be calculated by simple subtraction and expressed as a fraction (eg, 100% - 5% = 95% or 0.95).

To find the number of units of factor VIII needed to correct the factor VIII activity level, use the following formula:

Units factor VIII = (weight in kg)*(50 mL plasma/kg)*(1 U factor VIII/mL plasma)*(desired factor VIII level minus the native factor VIII level)

As an example, an 80-kg individual diagnosed with hemophilia with known 1% factor VIII activity level presents to the emergency department with a severe upper GI bleed. The correct dose of factor VIII to administer to the patient would be calculated as follows:

Units factor VIII = (80 kg)*(50 mL/kg)*(1 U factor VIII/mL)*(.99) = 3960.

The next dose should be administered 12 hours after the initial dose and is one half the initial calculated doses. Minor hemorrhage requires 1-3 doses of factor VIII. Major hemorrhage requires many doses and continued factor VIII activity monitoring with the goal of keeping the trough activity level at least 50%. Continuous infusions of factor VIII may be considered for major hemorrhage.

The specific factor product patients' use is often part of their individualized treatment plan. Patients will usually be well educated on their dosing/products. This information also can be found on institutional treatment center/blood bank databases.

Prophylactic administration of factor VIII is often recommended for pediatric patients with severe disease.

Other medicinal adjuncts to factor VIII (eg, desmopressin acetate, antifibrinolytics) often are useful in achieving hemostasis and can lessen the need for factor VIII infusion.

Antifibrinolytic agents, such as aminocaproic acid and tranexamic acid, are contraindicated as initial therapies for hemophilia-related hematuria originating from the upper urinary tract because they can cause obstructive uropathy or anuria.

Table 11. Suggested plasma factor peak level and duration of administration (when there is no significant resource constraint)

Type of hemorrhage	Hemophilia A		Hemophilia B	
	Desired level (IU dL1)	Duration (days)	Desired level (IU dL1)	Duration (days)
Joint	40–60	1–2, may be longer if response is inadequate	40–60	1–2, may be longer if response is inadequate
Superficial	40–60	2–3, sometimes	40–60	2–3, sometimes

muscle/no NV compromise (except iliopsoas)		longer if response is inadequate		longer if response is inadequate
Iliopsoas and deep muscle with NV injury, or substantial blood loss				
Initial	80–100	1–2	60–80	1–2
Maintenance	30–60	3–5, sometimes longer as secondary prophylaxis during physiotherapy	30–60	3–5, sometimes longer as secondary prophylaxis during physiotherapy
CNS/head				
Initial	80–100	1–7	60–80	1–7
Maintenance	50	8–21	30	8–21
Throat and neck				
Initial	80–100	1–7	60–80	1–7
Maintenance	50	8–14	30	8–14
Gastrointestinal				
Initial	80–100	7–14	60–80	7–14
Maintenance	50		30	
Renal	50	3–5	40	3–5
Deep laceration	50	5–7	40	5–7
Surgery (major)				
Pre-op	80–100		60–80	
Post-op	60–80	1–3	40–60	1–3
	40–60	4–6	30–50	4–6
	30–50	7–14	20–40	7–14
Surgery (minor)				
Pre-op	50–80		50–80	
Post-op	30–80	1–5, depending on type of procedure	30–80	1–5, depending on type of procedure

Table 12. Suggested plasma factor peak level and duration of administration (when there is significant resource constraint).

Type of hemorrhage	Hemophilia A		Hemophilia B	
	Desired level (IU dL1)	Duration (days)	Desired level (IU dL1)	Duration (days)
Joint	10–20	1–2, may be longer if response is inadequate	10–20	1–2, may be longer if response is inadequate
Superficial muscle/no NV compromise (except iliopsoas)	10–20	2–3, sometimes longer if response is inadequate	10-20	2–3, sometimes longer if response is inadequate
Iliopsoas and deep muscle with NV injury, or substantial blood loss				
Initial	20-40		15-30	1–2
Maintenance	10-20	3–5, sometimes longer as secondary prophylaxis during physiotherapy	10-20	3–5, sometimes longer as secondary prophylaxis during physiotherapy
CNS/head				
Initial	50–80	1–3	50–80	1–3
Maintenance	30–50	4–7	30–50	4–7

	20–40	8–14	20–40	8–14
Throat and neck				
Initial	30–50	1–3	30–50	1–3
Maintenance	10–20	4–7	10–20	4–7
Gastrointestinal				
Initial	30–50	1–3	30–50	1–3
Maintenance	10–20	4–7	10–20	4–7
Renal	20–40	3–5	15–30	3–5
Deep laceration	20–40	5–7	15–30	5–7
Surgery (major)				
Pre-op	60–80		50–70	
Post-op	30–40	1–3	30–40	1–3
	20–30	4–6	30–40	1–3
	10–20	7–14	10–20	7–14
Surgery (minor)				
Pre-op	40–80		40–80	
Post-op	20–50	1–5, depending on type of procedure	20–50	1–5, depending on type of procedur

Desmopressin

Desmopressin vasopressin analog, or 1-deamino-8-D-arginine vasopressin (DDAVP), is considered the treatment of choice for mild and moderate hemophilia A. It is not effective in the treatment of severe hemophilia. DDAVP stimulates a transient increase in plasma FVIII levels and results in sufficient hemostasis to stop a bleeding episode or to prepare patients for dental and minor surgical procedures. Other possible mechanisms of action are noted. A test dose should be performed. It can be intravenously administered at a dose of 0.3 mcg/kg of body weight in the inpatient setting. Its peak effect is observed in 30-60 minutes. A concentrated DDAVP intranasal spray is available for outpatient use. Its effectiveness is similar to that of the intravenous preparation, although its peak effect is observed later, at 60-90 minutes after administration. Patients should be advised to limit water intake during treatment and to avoid 3 consecutive daily doses to a prevent hyponatremia. Several doses of DDAVP may need to be infused every 12-24 hours before tachyphylaxis is observed. The major adverse effects of DDAVP include asymptomatic facial flushing and hyponatremia.

Management of bleeding episodes by site

Musculoskeletal bleeding. The most common sites of clinically significant bleeding are joint spaces. Weight-bearing joints in the lower extremities are often target areas for recurrent bleeding. Joint hemorrhage is associated with pain and limitation in the range of motion, which is followed by progressive swelling in the involved joint. Immobilization of the affected limb and the application of ice packs are helpful in diminishing swelling and pain. Early infusion upon the recognition of pain may often eliminate the need for a second infusion by preventing the inflammatory reaction in the joint. Prompt and adequate replacement therapy is the key to preventing long-term complications. Cases in which treatment begins late or causes no response may require repeated infusions for 2-3 days. Do not aspirate hemarthroses unless they are severe and involve significant pain and synovial tension. Some hemarthroses may pose particular problems because they interfere with the blood supply. Hip joint hemorrhages can be complicated by aseptic necrosis of the femoral head. Administer adequate replacement therapy for at least 3 days. Deep intramuscular hematomas are difficult to detect and may result in serious muscular contractions. Appropriate and timely replacement therapy is important to prevent such disabilities. Iliopsoas muscle bleeding may be difficult to differentiate from hemarthrosis of the hip joint. Physical examination usually reveals normal hip rotation but significant limitation of extension. Ultrasonography in the involved region may reveal a hematoma in the iliopsoas muscle. This condition requires adequate replacement therapy for 10-14 days and a physical therapy regimen that strengthens the supporting musculature. Closed-compartment hemorrhages pose a significant risk of damaging the neurovascular bundle. These occur in the upper arm, forearm, wrist, and palm of the hand. They cause swelling, pain, tingling, numbness, and loss of distal arterial pulses. Infusion must be

aimed at maintaining a normal level of FVIII. Other interventions include elevation of the affected part to enhance venous return and, rarely, surgical decompression.

Oral bleeding. Oral bleeding from the frenulum and bleeding after tooth extractions are not uncommon. Bleeding is aggravated by the increased fibrinolytic activity of the saliva. Combine adequate replacement therapy with an antifibrinolytic agent (epsilon-aminocaproic acid) to neutralize the fibrinolytic activity in the oral cavity. Topical agents such as fibrin sealant, bovine thrombin, and human recombinant thrombin can also be used. Hematoma in the pharynx or epiglottic regions frequently results in partial or complete airway obstruction; therefore, it should be treated with aggressive infusion therapy. Such bleeding may be precipitated by local infection or surgery. Administer prophylactic factor infusion therapy before an oral surgical procedure to prevent the need for further treatment.

Gastrointestinal bleeding. GI bleeds are unusual compared with those associated with von Willebrand disease and, therefore, require an evaluation for an underlying cause. Manage GI hemorrhage with repeated or continuous infusions to maintain nearly normal circulating levels of FVIII.

Intracranial bleeding. Intracranial hemorrhage is often trauma induced; spontaneous intracranial hemorrhages are rare. If CNS hemorrhage is suspected, immediately begin an infusion prior to radiologic confirmation. Maintain the factor level in the normal range for 7-10 days until a permanent clot is established. All head injuries must be managed with close observation and investigated by imaging such as CT scanning or MRI. If the patient is not hospitalized, instruct the patient and his or her family regarding the neurologic signs and symptoms of CNS bleeding so that the patient can know when to return for reinfusion.

Prophylactic factor replacement therapy

Prophylaxis is the treatment by intravenous injection of factor concentrate in order to prevent anticipated bleeding (see Table 13). Prophylaxis was conceived from the observation that moderate hemophilia patients with clotting factor level >1 IU/dl seldom experience spontaneous bleeding and have much better preservation of joint function.

Table 13. **Definitions of factor replacement therapy protocols**

Episodic (“on demand”) treatment	Treatment given at the time of clinically evident bleeding
Continuous prophylaxis Primary prophylaxis	Regular continuous* treatment initiated in the absence of documented osteochondral joint disease, determined by physical examination and/or imaging studies, and started before the second clinically evident large joint bleed andage 3 years**
Secondary prophylaxis	Regular continuous* treatment started after 2 or more bleeds into large joints** and before the onset of joint disease documented by physical examination and imaging studies
Tertiary prophylaxis	Regular continuous* treatment started after the onset of joint disease documented by physical examination and plain radiographs of the affected joints
Intermittent (“periodic”) prophylaxis	Treatment given to prevent bleeding for periods not exceeding 45 weeks in a year

* continuous is defined as the intent of treating for 52 weeks/year and receiving a minimum of an a priori defined frequency of infusions for at least 45 weeks (85%) of the year under consideration.

**large joints = ankles, knees, hips, elbows and shoulders.

Prophylaxis prevents bleeding and joint destruction and should be the goal of therapy to preserve normal musculoskeletal function. Prophylactic replacement of clotting factor has been shown to be useful even when factor levels are not maintained above 1 IU/dl at all times. It is unclear whether all patients should remain on prophylaxis indefinitely as they transition into adulthood. Although some data suggest that a proportion of young adults can do well off prophylaxis, more studies are needed before a clear recommendation can be made. In patients with repeated bleeding, particularly into target joints, short-term prophylaxis for four to eight weeks can be used to interrupt the bleeding cycle. This may be combined with intensive physiotherapy or synoviorthesis. Prophylaxis does not reverse established joint damage; however,

it decreases frequency of bleeding and may slow progression of joint disease and improve quality of life. Prophylaxis as currently practiced in countries where there are no significant resource constraints is an expensive treatment and is only possible if significant resources are allocated to hemophilia care. However, it is cost-effective in the long-term because it eliminates the high cost associated with subsequent management of damaged joints and improves quality of life.

Pain management

Acute and chronic pain are common in patients with hemophilia. Adequate assessment of the cause of pain is essential to guide proper management.

Pain caused by joint or muscle bleeding. While clotting factor concentrates should be administered as quickly as possible to stop bleeding, additional drugs are often needed for pain control (see Table 14). Other measures include cold packs, immobilization, splints, and crutches.

Post-operative pain. Intramuscular injection of analgesia should be avoided. Post-operative pain should be managed in coordination with the anesthesiologist. Initially, intravenous morphine or other narcotic analgesics can be given, followed by an oral opioid such as tramadol, codeine, hydrocodone, and others. When pain is decreasing, paracetamol/acetaminophen may be used.

Pain due to chronic hemophilic arthropathy. Chronic hemophilic arthropathy develops in patients who have not been adequately treated with clotting factor concentrates for joint bleeding. Treatment includes functional training, adaptations, and adequate analgesia. COX-2 inhibitors have a greater role in this situation. Other NSAIDs should be avoided. When pain is disabling, orthopedic surgery may be indicated.

Table 14. **Strategies for pain management in patients with hemophilia**

1	Paracetamol/acetaminophen If not effective
2	COX-2 inhibitor (e.g. celecoxib, meloxicam, nimesulide, and others) OR Paracetamol/acetaminophen plus codeine (3-4 times/day) OR Paracetamol/acetaminophen plus tramadol (3-4 times/day)
3	Morphine: use a slow release product with an escape of a rapid release. Increase the slow release product if the rapid release product is used more than 4 times/day

Surgery and invasive procedures

Surgery may be required for hemophilia-related complications or unrelated diseases. The following issues are of prime importance when performing surgery on persons with hemophilia. Surgery for patients with hemophilia will require additional planning and interaction with the healthcare team than what is required for other patients. A hemophilia patient requiring surgery is best managed at or in consultation with a comprehensive hemophilia treatment center. The anesthesiologist should have experience treating patients with bleeding disorders. Adequate laboratory support is required for reliable monitoring of clotting factor level and inhibitor testing. Pre-operative assessment should include inhibitor screening and inhibitor assay, particularly if the recovery of the replaced factor is significantly less than expected. Surgery should be scheduled early in the week and early in the day for optimal laboratory and blood bank support, if needed. Adequate quantities of clotting factor concentrates should be available for the surgery itself and to maintain adequate coverage post-operatively for the length of time required for healing and/or rehabilitation. If clotting factor concentrates are not available, adequate blood bank support for plasma components is needed. The dosage and duration of clotting factor concentrate coverage depends on the type of surgery performed. Patients with mild hemophilia A, as well as patients receiving intensive factor replacement for the first time, are at particular risk of inhibitor development and should be re-screened 4–12 weeks postoperatively. Careful monitoring for inihibitors is also advisable in patients with non-severe hemophilia A receiving continuous infusion after surgery. Infusion of factor concentrates/hemostatic agents is necessary before invasive diagnostic procedures such as lumbar puncture, arterial blood gas determination, or any endoscopy with biopsy.

Dental care and management

For persons with hemophilia, good oral hygiene is essential to prevent periodontal disease and dental caries, which predispose to gum bleeding. Dental examinations should be conducted regularly, starting at the time the baby teeth start to erupt. Teeth should be brushed twice a day with a medium texture brush to remove

plaque deposits. Dental floss or interdental brushes should be used wherever possible. An orthodontic assessment should be considered for all patients between the ages of 10–14 to determine if there are any problems associated with overcrowding, which can result in periodontal disease if left untreated. Close liaison between the dental surgeon and the hemophilia team is essential to provide good comprehensive dental care. Treatment can be safely carried out under local anesthesia using the full range of techniques available to dental surgeons. Infiltration, intra-papillary, and intra-ligamentary injections are often done under factor cover (20–40%) although it may be possible for those with adequate experience to administer these injections without it. Treatment from the hemophilia unit may be required before an inferior alveolar nerve block or lingual infiltration. Dental extraction or surgical procedures carried out within the oral cavity should be performed with a plan for hemostasis management, in consultation with the hematologist. Tranexamic acid or epsilon aminocaproic acid (EACA) is often used after dental procedures to reduce the need for replacement therapy. Oral antibiotics should only be prescribed if clinically necessary. Local hemostatic measures may also be used whenever possible following a dental extraction. Typical products include oxidized cellulose and fibrin glue. Following a tooth extraction, the patient should be advised to avoid hot food and drinks until normal feeling has returned. Smoking should be avoided as this can cause problems with healing. Regular warm salt water mouthwashes (a teaspoon of salt in a glass of warm water) should begin the day after treatment and continue for 5–7 days or until the mouth has healed. Prolonged bleeding and/or difficulty in speaking, swallowing, or breathing following dental manipulation should be reported to the hematologist/dental surgeon immediately. NSAIDs and aspirin must be avoided. An appropriate dose of paracetamol/acetaminophen every 6 h for 2–3 days will help prevent pain following an extraction. The presence of blood-borne infections should not affect the availability of dental treatment. Prevention of bleeding at the time of dental procedures in patients with inhibitors to FVIII or FIX requires careful planning.

VI. Plan and organizational structure of employment. See Appendixe 1.

VII. Materials of control and methodical providing of employment

VII.1 Materials of control for the preparatory stage of employment

Question for the control of initial level of knowledge's of skills and abilities:

1. Formulate determination of hemophilia and ITP.
2. Define etiology of hemophilia and ITP.
3. Specify the key links of pathogenesis of hemophilia and ITP.
4. Name the modern clinical classification of hemophilia and ITP.
5. Name the typical clinical signs of hemophilia and ITP.
6. Work out a plan of laboratory and instrumental inspection of patient with hemophilia and ITP.
7. Specify complications of hemophilia and ITP.
9. List principles of treatment of hemophilia and ITP.
10. Specify the basic groups of drugs are used for treatment of patients with hemophilia and ITP.

Tests for initial control:

1. What from the listed changes of laboratory indices are the most characteristic for ITP?

A. Increase of coagulation time
B. Increased free heparin level
C. Lowering of prothrombin level
D. *Lowering of platelets amount
E. Lowering of fibrinogen level

2. Second phase of hemocoagulation is:

A. *Formation of active thromboplastin
B. Blood clot retraction
C. Synthesis of prothrombin
D. Formation of thrombin
E. Formation of fibrin

3. What from the listed signs of hemorragic syndrome are the most characteristic for hemophilia?

A. *Posttraumatic bleeding, hemarthroses
B. Petechial skin rash, abdominal pain, hematuria
C. The spontaneous bleeding from mucous membranes
D. Papular and petechial skin rash that symmetric located on extremities
E. Nasal bleeding

4. The reason of development of hemophilia A is:
A. Infectious and inflammatory diseases
B. Congenital vascular disorders
C. Thrombocytopenia
D. *Deficiency of the VIII clotting factor
E. Deficiency of the IX clotting factor

5. What from the listed drugs are the basic in a conservative therapy of idiopathic thrombocytopenic purpura?
A. Blood transfusion
B. Heparin
C. Cryoprecipitate
D. *Glucocorticoids
E. Dicinon

6. What from the listed changes of laboratory indices are the most characteristic for idiopathic thrombocytopenic purpura?
A. *Increase of bleeding time by Dyuke
B. Increase of coagulation time
C. Decrease of bleeding time by Dyuke
D. Decrease of coagulation time
E. Increase of APTT

7. For hemophilia all signs of hemorragic syndrome are characteristic, except for:
A. Bleeding from mucus
B. Hematuria
C. Hemarthroses
D. *Cerebral haemorrhage
E. Hypodermic hematomas

8. The formation of hemostatic plug is related to:
A. Converting of fibrinogen into a fibrin.
B. Marginal position of leucocytes
C. Hemolysis of RBC.
D. Increasing of ESR.
E. *Platelets adhesion

9. At uncomplicated hemophilia there is the every symptom, except for:
A. Hemarthrose
B. Hemorragic syndrome
C. *Increased bleeding time by Dyuke
D. Coagulation disorders
E. Prolongation of recalcification plasma time

10. What type of bleeding is characteristic for thrombocytopenia?
A. *Petechial-ecchymosous
B. Hematomal
C. Vasculitous-purpura
D. Angiomatous
E. Mixed

Tests of the II level:

1. At a teenager 15 years, from a wound which appeared after extraction of tooth, the strong bleeding began. At additional collection of anamnesis, it is exposed that the hospitalized teenager is ill the hemophilia A. What drug is the most effective for treatment of such bleeding?

A. *Cryoprecipitate
B. Aminocapronic acid
C. Chloride of calcium
D. Vikasol
E. Ascorutin

2. At 16 years-old youth after conducting of inoculation there was the protracted bleeding from the place of injection, whereupon an intramuscular hematoma appeared. There is the exposed considerably promoted consumption of prothrombin and expressed lengthening of the activated partial thromboplastin time at the inspection. What disease does it follow to think about?

A. *Hemophilia
B. Werlhof's disease.
C. Schönlein-Henoch disease
D. Willebrand's disease.
E. Afibrinogenemia.

3. Youth 15 years suffers from pain in a right knee, moderate swelling of it, narrow-mindedness of motion. Pain arose up suddenly after an unsuccessful jump. Anamnesis: in childhood a patient had bruises on a body, bleeding from the small holes of teeth at the change of baby teeth. At the review of skin exposed bruises on buttocks, abdomen. Blood count: Er. $3,6x10^{12}$/l, Нв 108 g/l, L 9,8 $x10^{9}$/l, eos.-2%, bas.-1%, band cells-11%, segment.-52%, limph.- 28%, мон,- 6%, ESR -15 mm/h. What is diagnosis?

A. *Hemophilia
B. Hemolytic anemia
C. Thrombocytopenic purpura
D. Schönlein-Henoch disease
E. Willebrand's disease

4. In woman, 56 years, nasal bleeding was stopped with difficulty during hypertension stroke. It begin again in 6 hours, ear bleeding, blood in the vomiting, ecchymosis in the area of injections, oliguria and urine as “meat pigwashes” are appeared. Take a diagnosis.

A. Idiopathic thrombocytopenic purpura
B. Hemophilia
C. Disseminated intravascular coagulation
D. Randy-Osler's disease
E. Schönlein-Henoch disease

5. Patient, 50 years, used constantly fenilin 0,4 mg per day. During a week he has been marked hemorragic rash, bleeding from gums. Anamnesis: 5 years ago he was operated due to an aortal valvular disease, aortic valve replacement was made. Blood test: platelets - 220 $*10^{9}$/l, coagulation time - 25 minutes, bleeding time - 12 minutes, prothrombin index - 32%. What is diagnosis?

A. Hemophilia A
B. Hemophilia B
C. *Overdose indirect anticoagulants
D. Hemophilia C
E. Thrombocytopenia

6. Patient, 23 years, complains of bleeding from a nose, gums, hemorragic rash appeared 1 month ago. Objectively: petechial skin rash, positive “nip” test, the changes of internal organs are not revealed. Blood test: Hb – 105g/l, leucocytes - 5,4 *109/l, platelets - 11 *109/l, leucocytic formula is without pathological changes, bleeding time - 23 minutes. What is clotting disorder?

A. Willebrand's disease
B. Thrombocytopathy
C. Coagulopathy
D. *Idiopathic thrombocytopenic purpura
E. Disseminated intravascular coagulation, III phase

VII.2 Materials of the methodical providing of basic stage of employment

Professional algorithm of implementation of patient curation (reference card) for forming of practical skills and abilities

№	Tasks	Sequence implementation	Remark, warning in relation to self-control
1	To conduct the objective examination of patient with hemophilia	1. To conduct collection of complaints, anamnesis of disease. 2. Carefully to collect anamnesis of life of patient. 3. To conduct the review of patient. 4. To investigate the joints 5. To investigate a skin and mucus of patient.	To pay attention to the features, descriptions and terms of origin of hemorrhagic syndrome, anamnesis morbi of patient. To set the presence of risk factors leads to complication of hemophilia and ITP. To estimate the general state of patient, position in a bed, color and humidity of skin and mucus, presence of hematomas and hemorrhagic rash, edema of joints. To pay attention to the joints of patient. Hemophilic arthropathy: combination acute hemarthrosis (primary and recurrent) and chronic destructive osteoarthros. Determinate soft tissue changes (hyperplasia, thickening), periarticular tissue changes, subcutaneous hematomas
2	To formulate a previous diagnosis.	1 Formulate and preliminary diagnosis. 2. Substantiate all components of previous diagnosis on the basis of complaints, medical history and life, physical examination	Based on the current classification of hemophilia and ITP formulate a preliminary diagnosis and substantiate every component.
3	To estimate the indexes of additional laboratory and instrumental researches.	1. To estimate complete blood count. 2. To estimate urine test. 3. To estimate coagulogram: coagulation time, prothrombin time, APTT; time of bleeding by Duke. 5. To estimate the clotting factors level	To pay attention amounts of platelets, RBC, LBC. To pay attention of hematuria in combination with the attacks of kidney colic (formation of clots in urinary ways - in 15 - 30% of patients). To pay attention on the duration of coagulation time, prothrombine time, APTT (hemophilia A and B) at the normal index of bleeding time by Duke. To set the deficiency of clotting factors
4	To interpret information of images	1. To interpret X-ray images, CT scan MRI of joints.	To pay attention on the hemarthrosis

5.	To conduct differential diagnostics.	1. Consistently find similarities in the complaints, medical history of the disease and life, objective status, data, laboratory and instrumental methods of examination of the patient and with similar nosology. 2. Find the differences between the complaints, according to medical history and life, objective symptoms, results of laboratory and instrumental methods of research and patient with similar nosology. 3. Based on the identified differences exclude similar disease from the list of possible diagnoses. 4. To the differential diagnosis by the aforementioned algorithm with all nosology that have similar clinical signs with the patient. 5. Given the impossibility to exclude anemia from a list of possible diagnoses draw a conclusion the greatest likelihood of such a diagnosis.	Particular attention should be paid to the differential diagnosis of Rendu-Osler-Weber disease, Schönlein-Henoch disease, von Willebrand'sdisease, leukemia, lymphomas.
6.	1. Formulate a final clinical diagnosis. 2. Based on the diagnosis, analysis of additional laboratory and instrumental methods conducted differential diagnosis to justify all the elements of the final clinical diagnosis.	Based on the current classification of ITP and hemophilia formulate previous diagnosis indicating the stage and severity of exacerbations, complications of the underlying disease and concomitant diseases.	To formulate a final clinical diagnosis.
7.	To administer treatment a patient.	1. Life style recommendations. 2. To administer drugs, other methods of treatment.	To indicate the regime and diet. Considering the age, the severity of disease, presence of complications and concomitant pathology appoint modern medical treatment according to the ITP and hemophilia guidelines.

VII.3 Materials of control for the final stage of employment

Test of the III level (α=3). Differential diagnostics the diseases with hemorrhagic syndrome

Symptoms	Hemophilia A	ITP	Rendu-Osler-Weber disease	von Willebrand's disease	Schönlein-Henoch disease
1. Nasal bleeding	-	+	+	+	-
2. Types of hemorrhage • capillary (petechial-bruising) type	-	+	-	+	-
• Hematoma	+	-	-	-	-
• Mixed (capillary-hematomic) tupe	-	-	-	+	-
• Vasculitis, purpura	-	-	-	-	+
• Angiomatouse type	-	-	+	-	-
3. Protracted bleeding at traumas and medical manipulations	+	-+	-+	+	-
4. Hemarthrosis	+	-	-	+	-
5. Secondary rheumatoid arthritis	+	-	-	-	-
6. Hemorrhage to the soft tissues	+	-	-	+	-
7. Massive hematocelia	+	+	+-	-+	-+
8. Subarachnoid hemorrhage.	-+	+	+-	-+	-+
9. RBC, hemoglobin	↓ N	↓	↓	↓ N	↓
10. Platelets	N	↓	N	N ↓	N ↑
11. Hematuria	+	-	+	+-	+
12. APTT	↑	N	N	N ↑	N
13. Bleeding time	N	↑	N	N ↑	N
14. Coagulation time	↑	N	N	N	N
15. Prothrombin time	↑	N	N	N ↑	N
16. Ristomicin-induced platelet aggregation	N	N	N	↓	N

COAGULATION SCREENING TESTS

Investigation	Normal range	Disorders
Platelet count	150-400 × 10^9/l	Thrombocytopenia
Bleeding time	< 8 minutes	Thrombocytopenia Abnormal platelet function Deficiency of von Willebrand's factor Vascular abnormalities
Prothrombin time (PT)	12-15 seconds	Deficiency of factors II, V, VII or X
Activated partial thromboplastin time (APTT)	30-40 seconds	Deficiency of factors II, V, VIII, IX, X, XI, XII Heparin Antibodies against clotting factors Lupus anticoagulant
Fibrinogen concentration	1.5-4.0 g/l	Hypofibrinogenaemia

Task №1 (α=3).

A girl of 16 years is hospitalized with complaints of the nasal bleeding, rash on the skin of extremities, trunk. Anamnesis: she suffers on bronchial asthma from childhood. During last year she had frequent nasal bleeding at night. The worsening of the state she marked after chocolate abuse. Objectively: general state is heavy. There is asymmetrical, polychromic hemorrhagic rash (petechial, ecchimoses) on the extremities and

trunk. A liver and spleen are not enlarged. Blood count: Er.-3,6 x 10^{12}/l; Нв-80 g/l; CI - 0,8; reticulocytes - 12 %; platelets - 14 x 10^{9}/l; leucocytes - 5,9 x 10^{9}/l; eos.-10 %, band cells - 3%; segment. - 56 %; lymph. - 28%; mon. - 3%, ESR - 13 mm/h. Bone marrow aspirate: number of megakaryocytes increased.

1) What is your diagnosis?
2) Plan of examination.
3) Administer treatment.

Standard of answer:

1) Idiopathic thrombocytopenic purpura, acute phase.
2) Complete blood count, bleeding time by Duke, peripheral blood smear, test for antibodies to HIV, antiplatelet and antinuclear antibodies, Coombs test.
4) Hemostasis: dicinon 0,25g twice a day, aminocapronic acid 0,5 g twice a day. Basic therapy: prednisolone from 1 mg/kg/day (starting dose) to 2 mg/kg/day. Intravenous Rh immunoglobulin and anti-D immunoglobulin. Planned splenectomy.

Task №2 (α=3).

Patient, 19 years, complaints of the prolonged, severe bleeding. It occurs in 2 hours after tooth extraction. Anamnesis: repeated painful hematomas after slight traumas. He had hemarthrosis of right knee joint at the age of 14 (after the trauma). The grand-dad of patient had similar symptoms.

1) What is credible diagnosis?
2) Substantiate your clinical diagnosis.
3) Plan of examination.
4) Tactic of treatment.

Standard of answer:

1) Hemophilia.
2) Clinical manifestation after traumas and invasive medical procedures, data of family anamnesis
4) Complete blood count, peripheral blood smear. Coagulogram: activated partial thromboplastin time, cogulation time, prothrombin time. Clotting factors (VIII, IX, X, XI).
5) Factor VIII concentrate, epsilon-aminocaproic acid i/v. Fibrin sealant and human recombinant thrombin can also be used.

VIII. Materials of the methodical providing of self-study of students: a reference card is for organization of independent work of students with educational literature

Task	Instructions
To learn etiology of hemophilia and ITP	List the basic etiologic factors of hemophilia and ITP
To learn pathogenesis of hemophilia and ITP	To select the key links of pathogenesis of hemophilia and ITP
To learn the clinical manifestation of hemophilia and ITP	To set symptoms and clinical syndromes which enable to offer the previous diagnosis of hemophilia and ITP
To learn the diagnostic criteria of hemophilia and ITP	To make the structural scheme of disease
To learn the investigation (laboratory, instrumental)	List the basic diagnostic criteria of hemophilia and ITP according to data of investigations
To conduct differential diagnostics, set a final clinical diagnosis	Substitute the basic components of diagnosis in accordance with modern classification, and to conduct a differential diagnosis
To administer the individual treatment patient with hemophilia and ITP	Wright down the list of prescriptions include the regime, diet, drug therapy considering the age, the severity of disease, presence of complications and concomitant pathology

Tests for final control

1. Patient, 64 y.o., complains on ostealgia, sweating, general weakness, dizziness. Objectively: painful bones at percussion. Blood test: RBC-2,6 *10^12/l, Hb-89 g/l, CI-0,92, L-6.4 *10^9/l, e-1%, bas-0%, bands-4%, s-64%, l-29%. Platel.-170 *10^9/l. ESR-58 mm/h. General protein – 137 g/l. What examination method in this case is most informative for verification of diagnosis?
A. Research of bone marrow
B. Electrophoresis of serum proteins
C. X-ray of bones
D. Ionogram
E. Urine analysis

2. Young man suffers from severe pain in a right knee, slight swelling of it, limitation of motions, pain occurs suddenly after an unsuccessful jump. It is known from anamnesis, that in childhood a patient had bruises on a body, bleeding from the small holes of teeth at the change of baby teeth. At a review skins, discovered bruises on glutei, on the skin and stomach. Blood count: Hb 108 g/l, RBC 3.6 *10^12/l, L–9,8 *10^9/l, e-2%, bas-1%, bands-11%, s-52%, l- 28%, m- 6%, ESR -15 mm/h. Your diagnosis is:
A. Hemophilia
B. Hemolytic anemia
C. Thrombocytopenic purpura
D. Hemorrhagic vasculitis
E. Hemoglobinopathy

3. For a patient after a quinsy pain appeared in tube bones, general increase of lymphonodes, hepatolienal syndrome. Blood test: RBC- 3,0 *10^12/l, Hb – 80 g/L, L – 18 *10^9/l, blasts- 90%, lymphocytes - 46%, thrombocytes – 50 10^9/l, ESR - 65 mm/h. Your diagnosis is:
A. Acute lymphoblastic leukemia
B. Chronic lympholeukemia
C. Chronic myeloleukemia
D. Myeloma
E. Acute myeloblastic leukemia

4. Patient is on dispensary account with a diagnosis: Hemophilia A, severe form. He was admitted to the hospital with haemarthrosis of right knee. What type of therapy is indicated to the patient?
A. Cryoprecipitate in a dose 20 U/kg per day
B. Haemotransfusion
C. Chemotherapy
D. Antibacterial therapy
E. Hormone therapy

5. In patient of 42 y.o. in 2 months after acute respiratory disease appeared a general weakness, subfebrility, a skin is pale, spleen is enlarged on 4 sm. Blood analysis: RBC-2.9 10^12/l, Hb–90 g/L, CI-1.0; L-3.3 10^9/l, blasts–31%, myelocytes 0.5%, metamyelocytes-0.5%, b-4%, s-32%, e-2%, lymph-22%, monocytes-8%, tr.-60 10^9/l, ESR 25 mm/h. What is the initial diagnosis and what additional examination methods are necessary to prescribe?
A. Chronic myeloleukemia, puncture of bone marrow
B. Acute leukemia, cytochemical examination
C. Erythremia, hematocrit
D. Chr. lympholeukemia, puncture of bone marrow
E. Myeloma, blood biochemical analysis

6. Select the most characteristic clinical symptoms of the 2 stage of chronic lympholeukemia:
A. Increase of lymphatic nodes
B. Hemorrhagic syndrome
C. Hemolytic crisis
D. Splenohepatomegaly
E. All listed

8. In hemogramme revealed followings indexes: Hb - 62 g/l; RBC - 2,1 10^12/l; CI - 1,0; reticulocytes - 3%; leucocytes - 16,0 10^9/l; eos. 2%; bas - 0%; b - 1%; s - 4%; m - 2%; lymph - 91%; ESR - 64 mm/h. In a myelogram - 91% of lymphoblasts. What diagnosis is most probable due to laboratory indices?

A. Acute lymphoblastic leukemia
B. Hemolytic anemia
C. Acute myeloblastic leukemia
D. Werlhof's disease
E. Sepsis

9. In patient, 19 y.o., in a peripheral blood test is discovered: L – 4.2 10^9/l, Hb – 50.0 g/L, RBC – 2.5 10^12/l, thromb – 80.0 10^9/l, blasts - 47%, segm. neutrophils - 11%, monocytes - 10%, lymphocytes - 32%. What primary additional examination methods are necessary for diagnosis?

A. Cytologic research of bone marrow
B. Cumbs' test, liver function tests
C. Proteinogram, coagulogram
D. Electrolytes level in blood and urine
E. Uric acid blood level

10. To the doctor-hematologist the patient appealed with the symptoms of lacunar quinsy, symptoms of stomatitis, bleeding of gums. He is ill during 20 days. Traditional antibacterial therapy is ineffective. In blood analyses: RBC-3,5 10^12/l, Hb-102 g/L, CI-0,9, L-14,0 10^9/l, thromb.-100,0 10^9/l, blasts-18%, b-4%, s-18%, m-4%, l-56%, ESR-38 mm/h. What initial diagnosis can be formulated?

A. Acute leukemia
B. Chronic leukemia
C. Lymphogranulomatosis
D. Lymphosarcoma
E. Tuberculosis

11. In a patient it is revealed enlargement of jugular and axillary lymphatic nodes, size - 6,0x7,0 sm, consistence – softly-elastic, a liver comes forward from under a costal arc on 5 sm, spleen - on 8 sm, at palpation – sensible; sweating, weakness, weight loss. Patient is ill during 3 months. Blood analysis: Hb-112 g/L, CI-0,9, L-12 10^9/l, thrombocytes-220,0 10^9/l, ESR-20 mm/h, b-1%, s-8%, m-2%, l-89%, Botkin-Gumprekht's cells - in great quantity. What is the initial diagnosis?

A. Chronic lympholeukemia
B. Acute lympholeukemia
C. Acute myeloleukemia
D. Lymphosarcoma
E. Mononucleosis

12. In what leukemia a basophil -eosinophil association may be revealed?

A. Acute myeloblastic
B. Chronic myeloleukemia
C. Chronic lympholeukemia
D. Erythremia
E. Chronic erythromyelosis

13. What amount of blast cells in puncture material of bone marrow is acceptable in the period of clinico-hematological remission?

A. 4%
B. 5%
C. 8%
D. 10%
E. 15%

14. What examination method is necessary to confirm a diagnosis of neuroleucemia?

A. Sternal puncture
B. Trepanobiopsy
C. Liquor test
D. Computer tomography

E. Blood test

15. What variant of acute leukemia is the most frequent in adults?

A. Lymphoblastic
B. Myeloblastic
C. Monoblastic
D. Undifferentiated
E. Promyelocytic

16. What laboratory sign is the main in diagnostics of acute leukemia?

A. Leucopenia
B. Leucocytosis
C. Anemia
D. Thrombocytopenia
E. Blastemia

17. At what disease blast cells and “hiatus leucemicus” are present in a peripheral blood test?

A. Chronic myeloleukemia
B. Chronic lympholeukemia
C. Lymphogranulematosis
D. Myeloma
E. Acute leukemia

18. What changes of peripheral blood are characteristic for chronic lympholeukemia?

A. Leucopenia
B. Eosinophilia
C. Lymphopenia
D. Leucocytosis, absolute lymphocytosis
E. All incorrect

19. Systemic enlargement of lymphatic nodes is characteristic for:

A. Hypoplastic anemia
B. Myeloma
C. Rendu-Osler-Weber 's disease
D. Addison-Biermer's anemia
E. Chronic lympholeukemia

20. Specify the basic method of treatment of acute leukemia:

A. Polychemotherapy
B. Antibiotic therapy
C. Glucocorticoid therapy
D. Hemotransfusion
E. Leucopheresis

21. Specify the most frequent clinical symptom of chronic myeloleukemia:

A. Fever
B. Bleedings
C. Enlargement of lymphatic nodes
D. Enlargement of liver
E. Enlargement of spleen

22. In what disease we may see hyperleucocytosis with absolute lymphocytosis?

A. Acute leukemia
B. Chronic lympholeukemia
C. Tuberculosis
D. Whooping-cough
E. Agranulocytosis

23. Patient 24 years old complains on weakness, fever, jaundice. Objectively: t-38,50C, BP – 100/60 mmHg, PS - 102/min. Skin is pale with an icteric tint. Abdomen is soft, painless. A liver comes forward on 2 sm by linea medioclavic. dextra, a spleen comes forward on 1 sm from under left subcostal space. In blood: RBC - 2,8x10^12/l, Hb - 92 g/L, Reticulocytes - 26\%. What is the most probable initial diagnosis?

A. Hemolytic anemia

B. Acute post-hemorrhagic anemia
C. Acute hepatitis
D. B12-deficiency anemia
E. Aplastic anemia

24. In which from the listed anemia does a microspherocytosis take place?
A. Fankoni's
B. Markiafavi-Mikeli's
C. Addison-Biermer's
D. Minkowsky-Shauffard
E. Cooley's

25. In what anemia is an increases of reticulocytes in peripheral blood may be revealed?
A. Iron-deficiency
B. Megaloblastic
C. Hypoplastic
D. Hemolytic
E. Metaplastic

26. Person of 52 complains on dry cough, dyspnea, retrosternal pain, sweating at night, itch of skin. Objectively: left-side neck and supraclavicular lymphonodes are increased. T-37,4 by Celsius. Blood test: RBC-4,0 tera/L, Hb-135 g/L, CI-0,98, L-10,6 giga/L, e-2%, bas-1%, b-9%, s-52%, l-31%, m-5%. Chest X-ray - mediastinal lymphonodes are increased. What is the most probable diagnosis?
A. Lymphogranulomatosis
B. Sarcoidosis
C. Infectious mononucleosis
D. Lung cancer
E. Chronic lympholeukemia

27. Patient of 52 complains on dry cough, dyspnea, retrosternal pain, sweating at night, skin itch. Objectively: left-side neck and supraclavicular lymphonodes are increased. t-37,4. Blood test: RBC-3,7 tera/L, Hb-115 g/L, CI-0,98, L-15,6 giga/L, e-1%, bas-1%, b-5%, s-52%, l-38%, m-3%. What method of research will allow verification of diagnosis?
A. Cytohistological research of tissue of lymphonode
B. Cytochemical research of peripheral blood
C. Cytological research of bone marrow
D. Sonography of liver and spleen
E. Chest X-ray

28. Patient, 67 y.o., complains on general weakness, sweating, ostealgia. Skin – pale, peripheral lymphonodes are not increased. t-36.7. Percussion - painful bones are mentioned. Blood test: RBC-2,5 tera/L, Hb-85 g/L, CI-0,97, L-7.1 giga/L, e-2%, bas-0%, b-5, s-61, l-32. Tr.-156 giga/L. ESR-84 mm/h. General protein - 148 g/L. Protein in urine is 3 g/L. Most probable diagnosis is:
A. Multiply myeloma
B. Hypoplastic anemia
C. Chronic glomerulonephritis, nephrotic syndrome
D. Amyloidosis of kidneys, nephrotic syndrome
E. Kidney cancer

29. The patient of 23 y.o. complains on subfebrility, sweating at night, itch of skin, weight loss – 8 kg during half a year, increase of lymphatic nodes in a supraclavicular area. What examination method will give a possibility to put final diagnosis?
A. Histological research of puncture material of lymphatic node
B. US of liver and spleen
C. Chest CT-scan
D. Chest X-ray
E. Tomography of lymphatic nodes of mediastinum

30. Patient D. 24 y.o., complains on dry nightly cough, expressed sweating, itch of skin, weight loss on 10 kg Objectively: skin is pale, percussion sound is considerably shortened in a interscapular area, breathing is

of vesicular, clean. X-ray: polycyclic increase of lymphonodes of mediastinum. Mantu's test - negative. What disease do you can suppose first of all?
A. Lymphogranulomatosis
B. Sarcoidosis
C. Tuberculosis lymphadenitis
D. A central cancer of lungs
E. Atopic dermatitis
31. The patient 25 y.o. complains on enlargement of lymphonodes on necks, skin itch, sweating, fever up to 39.0. Objectively: cyanosis, swollen neck, a liver and spleen not increased, lymphonodes 1,5 - 2 sm in diameter is soldered with surrounding tissue. In puncture material of lymphonodus – Reed-Sternberg cells. What is the initial diagnosis?
A. Lymphogranulomatosis
B. Chronic lympholeukemia
C. Infectious mononucleosis
D. Lymphosarcoma
E. Metastases in lymphonodes
32. A teenager 15 years, from a wound which appeared after extraction of tooth, severe bleeding began. By additional anamnestic data, it was revealed that patient has hemophilia A. he was hospitalized immediately. What preparation is most effective for treatment of such bleeding:
A. Cryoprecipitate
B. Aminocapronic acid
C. Calcium chloride
D. Vikasol
E. Ascorutin
33. Patient, 20 y.o., was admited to the hospital with bleeding from a sword-cut, which lasts during 4 hours. Objectively: skin is pale, bandage impregnated with blood on left leg. A right knee-joint is deformed, motions in it are limited. The brother of patient suffers from Hemophilia A. Hb - 42 g/L, bleeding time by Duke - 3 min, time of coagulation of blood by Lee-White - 20 min. Blood does not coagulate. Your urgent care:
A. Intravenous stream injection of cryoprecipitate
B. Intramuscular injection of cryoprecipitate
C. Intravenous dropper of cryoprecipitate
D. Intravenous injection of epsilon-aminocapronic acid
E. Transfusion of thromboconcentrate
34. Patient of 50 y.o. anticoagulant-dependant. Takes constantly fenilin 0,4 mg OD. Within a week mentioned hemorrhagic signs on the skin, bleeding from gums. Anamnesis: 5 years ago was operated because of aortic defect, valve prosthesis was conducted. Blood test: thrombocytes - 220 giga/L, time of blood coagulation - 25 min., bleeding time - 12 min., prothrombin index - 32%. What is the diagnosis?
A. Overdosage of indirect anticoagulants
B. Hemophilia A
C. Hemophilia B
D. Hemophilia C
E. Thrombocytopenia
35. Patient of 21 complains on nosebleed, ash, hemorrhagic signs on the skin, which appeared 1 month ago. Objectively: on the skin of petechial rash, positive test of nip, changes of internal organs are not revealed. Blood test: Hb – 105 g/L, leucocytes 5,4 giga/L, thrombocytes 11 giga/L, leukocyte formula without pathological changes, time of bleeding 23 min. What is the diagnosis?

A. Idiopathic thrombocytopenic purpura
B. Willebrand's disease
C. Trombocytopathy
D. Coagulopathy
E. DVC-syndrome, III phase

36. To traumatology department delivered 12 years old boy which at playing football got the trauma of leg. Complains on acute pain in a right knee-joint. A child is ill by hemophilia. It is more expedient to begin urgent care from infusion of:
A. Plasma
B. Dicinon
C. Vikasol
D. Cryoprecipitate
E. Trombocytic mass

37. A girl of 13 y.o. complains on prolonged and abundant menstruation, general weakness. At a review the general state is severe, on all the body hemorrhagic rash - ecchymoses and petechies, on mucus - hemorrhages. He was 2 weeks ago ill on acute respiratory viral infection and received sulfanilamides. What is the most probable explanation of child's state?
A. Thrombocytopenic purpura
B. Hemorrhagic vasculitis
C. DVC-syndrome
D. Meningococcemia
E. Hemophilia B

38. Patient suffers from hemophilia A, harmed a knee, after it appeared swollen and hematoma in the area of trauma. What prescription will be most effective in this case?
A. Cryoprecipitate
B. Aminocapronic acid
C. Fresh-frozen plasma
D. Dicinon
E. Vitamin K

39. For a patient of 55 during a clinical review first found out small leucocytosis, absolute lymphocytosis due to mature lymphocytes; Gumprecht's shadows. A patient does not have complaints. In a myelogram there is acute increasing of lymphocytic metaplasia (90%) and decline of other sprouts of haemopoesis. What hematological disease takes place?
A. Chronic lympholeukemia
B. Acute lympholeukemia
C. Chronic myeloleukemia
D. Leucemoid reaction
E. Acute lymphoblastic leukemia

40. In which from the listed diseases does the expressed absolute lymphocytosis take place?
A. Lymphogranulematosis
B. Chronic lympholeukemia
C. Lymphosarcoma
D. Tuberculosis of lymphatic nodes
E. Myeloma

41. The patient, 36 y.o., complains on the dyspnea, shedding hair, tachycardia. Objectively: PS – 100/min., systolic murmur on apex; a liver and spleen are not enlarged. Blood test: RBC-2,7 tera/L, Hb-84 g/L, CI-0.86, reticulocytes-1\%, eos.-2\%, pal.-3\%, segm.-64\%, lymph.-26\%, mon.-5\%, ESR-17 mm/h. Iron of serum of blood - 7,3 mmol/L. Your diagnosis is:
A. Iron deficiency anemia
B. Syderoachrestic anemia
C. B12- folate deficiency anemia
D. Autoimmune hemolytic anemia
E. Aplastic anemia

42. A patient of 18 y.o., complains of periodic appearance of jaundice, weakness, heaviness in left subcostal area. Objectively: lymphonodes are not increased, liver near the edge of costal arc, spleen + 3 sm below costal arc. Blood test: RBC-2,7 tera/L, Hb-84 g/L, CI-0,96, reticulocytes-18\%, erythrocariocytes, microsferocytes. Non-direct bilirubin - 32 mkmol/L, in urine - hemosiderin, serum iron - 23,5 mmol/L. Your diagnosis is:
A. Minkowsky-Shauffard anemia

B. Autoimmunous hemolytic anemia
C. Sideroachrestic anemia
D. Hypoplastic anemia
E. B12-folate-deficiency anemia

43. The patient, 66 years, complains of the dyspnea, pain in tongue tip, paresthesia of hands. Operated concerning the gastric bleeding. Objectively: papilla of tongue are smoothed out, PS - 100 /min., systolic murmur above an apex, a liver and spleen are not increased. Neurological status: violations of sensitiveness, tendon reflexes are D=S. Blood test: RBC-2,7 tera/L, Hb-84 g/L, CI-1,2, reticulocytes-1%, eos.-2%, pal.-3%, segm.-64%, lymph.-26%, mon.-5%, ESR-17 mm/h. Macrocytes. Serum iron - 17,3 mkmol/L. Diagnosis is:

A. B12-folate-deficiency anemia
B. Autoimmune hemolytic anemia
C. Sideroachrestic anemia
D. Hypoplastic anemia
E. Minkowsky-Shauffard anemia

44. Patient U., 42 y.o., complains on general weakness, dyspnea, dizziness. Hairs got white during a year, nails began to exfoliate, taste changed. About 5 years is on a clinical supervision at a gynecologist concerning a fibromyoma of uterus. Blood test: RBC - 3.0 tera/L, Hb - 86 g/L, CI - 0.8, retik. - 7%, tr. - 160 giga/L, leuc. - 5.0 giga/L, eos. - 2%, pal. - 3%, segm. - 63%, lymph. - 28%, mon. - 4%, anizo-, microcytosis, ESR - 10 mm/h. What form of anemia does it follow to think about?

A. Iron deficiency
B. Hypoplastic
C. B12-folate deficiency
D. Autoimmune hemolytic
E. Minkowsky-Shauffard

45. Patient, 24 y.o., was directed on consultation to the hematologist due to recurrent icterus, splenomegaly. Blood test: RBC - 3.1 tera/L, Hb - 108 g/L, CI - 1.0, reticul. - 15%, diameter of RBC- 5.0 mcm, gen. bilirubin - 65 mcmol/L, indirect - 60 mcmol/L, direct - 5.0 mcmol/L. Contain of sterkobilin is increased in faeces and urine. Your initial diagnosis:

A. Minkowsky-Shauffard anemia
B. Gilbert's disease
C. Addison-Biermer anemia
D. Thalassemia
E. Marchiafava-Micheli disease

46. In young woman an internist diagnosed an anemic syndrome which appeared due to polymenorrhea during a year and exception of meat from the meal. General state of middle severety. In a clinical blood test: RBC - 1,8 tera/L, Hb - 62 g/L, CI - 0,87, leuc. - 3,8 giga/L, tr. - 160 giga/L, ESR - 26 mm/h. Content of serum iron - 6.8 mcmol/L. What is medical tactic in this case?

A. Reception of tablet iron drugs
B. Transfusion of RBC mass
C. A reception of preparations of iron for parenteral injection
D. Application of preparations of human erythropoietin
E. All listed

47. For a 68-years-old patient which suffers from CAD, the attacks of retrosternal pain becomes more frequent, increased demand of nitroglycerine, the dyspnea appeared at the insignificant physical exertion. ECG is without dynamics. In a blood test: RBC - 2,4 tera/L, Hb - 70 g/L, CI - 1.2, leuc. - 3,8 giga/L, tr. - 130 giga/L, ESR - 26 mm/h. A patient refuses from inspection of bone marrow. What prescription is necessary in this situation?

A. Vitamin B12 intramuscular injections
B. Drugs of iron orally
C. Increase of daily dose of nitraes
D. Transfusion of RBC
E. Parenteral prescription of iron drugs

48. The patient, 50 y.o., complains on general weakness, dizziness, heaviness in the upper half of abdomen, paresthesia of finger-tips of upper and lower extremities. Objectively: a skin is icteric, tongue of raspberry color, smooth and shiny, hepatomegalia. In blood: Hb - 90 g/L, RBC - 2,3 tera/L, rc. - 0,2%, CI - 1,2, macrocytosis; Zholli's bodies, Kebot's rings. What method of treatment will be most expedient?

A. Application of Vitamin B12
B. Application of Desferal
C. Blood transfusion
D. Use of iron drugs
E. Application of Prednisolone

49. A woman mentioned a general and muscular weakness, dyspnea, dizziness, fragility of hairs and nails, desire to eat a chalk. In anamnesis are fibromyoma of uterus. Blood test: RBC 2,8 tera/l, hemoglobin 105 g/L, color index 0,78, anisocytosis. What additional research will help to verify a diagnosis?

A. Serum iron
B. Amount of B12 in blood
C. Osmotic resistance of RBC
D. Coagulogram
E. Proteinogram

50. A patient complains on the loss of appetite, sense of heaviness in epigastria, diarrhea. A skin is pale and icteric, tongue of raspberry color, smooth, brilliant, at palpation pain in epigastria. Blood test: RBC 2,5 tera/L, Hb-96 g/L, C.I.-1,2, L.-2,9 giga/L, ESR-30 of mm/h., there are Zholli's bodies, Kebot's rings. What preparation does it follow to begin treatment from?

A. Cyanocobalamin
B. Tardiferron
C. Globeron
D. Ferrum-lek
E. Ferroplex

51. A patient obtained the icterus of skin and mucosa after the reception of Dopegit, spleen was increased. Blood test: RBC-2,3 tera/L, Hb-72 g/L, C.I. 0,84, L-15 giga/L, reticulocytes - 26%. Non-direct bilirubin in the serum of blood - 37 mcmol/L. The level of stercobilin is enhanced in urine and faeces. What blood test will help to verify a diagnosis?

A. Osmotic resistance of RBC
B. A content of B12 in blood
C. Serum iron
D. Coagulogram
E. Proteinogram

52. Patient, 39 y.o., complains on periodic dizziness, enhanced fatigueability, ear noise. Objectively: skin and visible mucus are pale. PS - 100 /min.. BP is 85/45 mmHg.. Cor - tones are rhythmic, sinus tachycardia. In blood: RBC - 2,2 giga/L, Hb - 90 g/L, serum iron - 7 mcmol/L, total iron blood capacity - 42,6 mcmol/L. What preparations does it follow to begin treatment from?

A. Iron drugs orally
B. Iron drugs intravenously, intramuscularly
C. Prescription of aminocapronic acid, dicinon, vikasol
D. Transfusion of erythromass
E. Transfusion of fresh-frozen plasma

53. Patient of 27 complains of dizziness, weakness in muscles, nausea, decline of appetite, dryness of skin, fragility of nails and hair. He is ill for closely half-year (after a birth of child). Objectively: skin and mucosa are pale. P=80 per min., rhythmic. Tones of heart are hyposthenic, systolic noise on the apex of heart. Stomach is soft, painless at palpation. At an additional inspection: Hb-80g/L; RBC-2,6 tera/L, CI-0,8. Anisocytosis, poykilocytosis: reticulocytes – 1/%. Content of iron in blood - 6,8 mkmol/L. What treatment one can appoint to patient?

A. Peroral reception of preparations of iron
B. Fresh blood transfusion
C. Transfusion of mass of RBC
D. Parenterally prescription of preparations of iron

E. Parenterally prescription of vitamins of group B

54. A 40-years-old woman who suffers menorrhagias complains of twinkling of "flies" before eyes, dizziness, dryness of skin, shedding hair. At inspection: pallor of skin and mucosa. Ps-100 per min. rhythmic, I tone on an apex is increased, systolic noise above all of points of heart. Hb-90 g/L, RBC-3,3*10/9/L, CI-0,7, leuc.-3,1*10/9/L, e-2%, p-3%, s-70\%, l-25\%, m-10\%, hypochromia of RBC, anisocytosis, microcytosis, serum iron-7,2 mcmol/L. What does the prophylaxis of disease consist of?

A. Iron drugs per os
B. Enough diet
C. Cyancobalamin
D. Hemotransfusion
E. Polyvitamins

55. 42-years-old woman, suffering from menorrhagias, complains of “flies” before eyes, dizziness, dryness of skin, fragerity of nails, psilosis.. At an inspection: pallor of skin and mucosa. Pulse - 100 per a minute, rhythmic, I tone on the apex of weakned, sistolic noise above the all points of heart. Hb - 90 g/L, RBC- 3,3 tera/L, C.I. - 0,7, leucocytes - 9,8 • 10^9/L, eosisinophills - 2%, band. - 3%, segm. - 70%, lymphocytes - 25%, monocytes – 10%, gipochromia of RBC, anisocytosis, microcytosis. What diagnostic is most for certain?

A. Iron deficiency anemia
B. B12-folate deficiency anemia
C. Acute post-hemorrhagic anemia
D. Aplastic anemia
E. Erythremia

56. At admission to in-patient department, patient C.of 44 years old complains of a general weakness, fasterned heartbeat, dyspnea at the physical exertion. “Ulcer anamnesis” - 20 years. Objectively: RR - 19 in a minute, pulse - 100 beats per minute, BP is 110/70 mm hg.. Skin is pale, dry. Nails are shineless, serrated, with transversal strings, hairs easily spoiled. Angular stomatitis. Cardiac tones are muffled, systolic noise above the apex of heart. In blood: RBC- 3,9 • tera/L, Hb - 90 g/L, reticulocytes - 0,8%; leucocytes - 4,2 x 10^9/L; eosinophils - 1%; band. – 1%; s - 53%; lymphocytes - 36%; monocytes - 9%; ESR - 20 mm/h. What anemia had a patient obtained?

A. Iron deficiency
B. Acute post-hemorrhagic
C. B12-deficiency
D. Folate-deficiency
E. Hemolytic

57. Patient A., 58 years old complains of risen fatigueability, fasterned heartbeat, dizziness, numbness of extremities and “ants” on skin, complains of a weakness. During many years is ill chronic gastritis. Objectively: skin is pale, light icterus; atrophy of papilla of tongue. Cardiac tones are muffled, systolic noise above the apex of heart. In blood: RBC- 1,6 x tera/L, Hb - 64 g/L; thrombocytes - 48 x 10^9g/L; leucocytes -3 x 10^9/L; eos. - 1%; band. - 1%; segm. - 39%; lymphocytes - 52%; monocytes - 8%; ESR - 20 mm/h, macrocytosis. What anemia did develop in patient?

A. B12-deficiency
B. Acute post-hemorrhagic
C. Iron deficiency
D. Folate-deficiency
E. Hemolytic

58. Patient of 28 years, in the past marked a weakness, periodically occuring light icterus skin. After the strong supercooling there was a chill, pain in muscles, and also in the upper half of stomach. Within a day - moderate icterus, dark excrement and urine. At research the moderate increase of liver and spleen, icteric of skin and mucosa, are determined. Blood test: hemoglobin - 80 g/L, erythrocytes of 2,8xtera/L, colour index 0,8, thrombocytes of 230x10^9/L, leucocytes of 9,5x10^9/L (formula is without changes). ESR - 20 mm/h, bilirubin - 77,0 mcmol/L, direct - 8,6 mcmol/L. What disease is the most probable:

A. Hemolytic anemia
B. Exacerbation of chronic cholecystitis
C. Acute infectious disease

D. Iron deficiency anemia
E. Chronic hepatitis

59. Patient of 20 years old during the last 2 months obtained an increasing weakness, sanguifluousness (skin hemorrages, nose-bleeding), subfebril temperature. Lymphatic nodes, liver and spleen, are not increased. Blood test: hemoglobin - 50 g/L, erythrocytes of 1,5xtera/L, C.I. 1,0 leuc. 1,8X10^9/L, b.- 1%, s.- 38%, e- 1%, l.- 55%, m.- 5%, tr. 30*10^9/L, ESR - 60 mm/h. What is initial diagnosis?

A. Aplastic anemia
B. Acute leukemia
C. Iron deficiency anemia
D. Hemolytic anemia
E. B12-deficiency anemia

60. Patient of 57, turned to clinic with complaints of a weakness, fatigue, head ache, dizziness, noise in ears, rising temperature to subfebril, feeling of burning on the end of tongue, hardness in swallowing of meal, feeling of "crawl of ants", numbness of hands, feet, hypotaxia in motions. He is ill for more than 5 years. Objectively: state of middle hardness, a skin is pale, of the lemon tint. Heart: tones are hyposthenic, systolic noise on an apex, tachicardia. AT 110/65 mm hg.. Stomach at palpation is soft, a little painful in an epigastric area, a liver is increased on 4 sm, the surface of it is smooth. A spleen on 2 sm comes forward from under left hypochondrium. Blood count: RBC-1,8xtera/L, Hb- of 59g/L, CI- 1,3, reticul.- 2\%, tromb- 120x109/L, megaloblasts 2 : 100, leuc- 2,2x10^9/l, youn.-1%, b-8%, s-45%, lymph.-40%, mon-5%, ESR- 30мм/h. Anisocytosis, poicilocytosis, macrocytes, Zholi bodies, Kebot rings, macropolycytes. Your diagnosis is:

A. B-12-deficiency anemia
B. Minkowsky-Shauffard disease
C. Iron deficiency anemia
D. Hypoplastic anemia
E. Hemolytic anemia

61. A woman of 35 complains of a general weakness, crabbiness, dryness of skin, fragility of nails, shedding hair. Objectively: skin and visible mucus are pale, Ps-96 per a minute, AT 100/60 mm. Blood count: Hb- 70g/L; RBC-3,4; CI-0,7; ret-2%; leck-4,7; eosis-2%, b-3%; s-64%, lymph-26%; mon-5%; ESR-15мм/h; Serum iron-7,3 mcmol/l; general protein-70g/l. What factor deficiency leads to disease?

A. Serum iron
B. Folate acid
C. Cyancobalamin
D. Protein of blood
E. Osmotic resistance of RBC

62. Patient of 42 complains of a general weakness, fatigue, nausea, decline of appetite, diarrheas, paresthesias in feet. For 12 years worked as a teacher, last 2 years is a laboratory assistant of chemical laboratory, where has a contact with petrol, benzol, acetone. Skin covers and visible mucosa are pale, scleras are subicteric. Pulse 96/min, BP-140/80. Tones of heart are rhythmic, muffled. Breathing of vesicular. Tongue - brightly red, smooth, with obsolete papillas. A stomach is soft, painfull in an epigastrium. The edge of liver comes forward from under a costal arc on 3 sm, close-settled, painful. In neurological status: tendon reflexes are evenly enhanced, hypesthesia in type of socks. Blood test: Hb-110 g/L, RBC-2,8xtera/L, L-4,6x10^9/L, megaloblasts - 2%, megacariocytes - 4%, b - 4%, s.-52%, lymph.-26%, mon.-12%, macro-, aniso- and poycilocytosis, Tr -156x10^9 /L, ESR-26 mm/h. Gastric Ph-metry specifies on achilia. Fibrogastroscopy: atrophy, polypus of stomach. Specify initial diagnosis:

A. B12-folate-deficiency anemia
B. Gastrogenic iron deficiency anemia
C. Hypoplastic anemia
D. Hemolytic anemia
E. Chronic intoxication by benzol

63. Enlargement of spleen in the initial stage of disease in adults is characteristic for:

A. Hemolytic anemia
B. Iron deficiency anemia
C. Chronic hepatitis

D. Chronic lympholeukemia
E. B-12-deficiency anemia

64. Severe general weakness quite often is an early sign of:
A. Iron deficiency anemia
B. Hemolytic anemia
C. Chronic gastritis
D. Chronic lympholeukemia
E. Acute lympholeukemia

65. For iron deficiency is characteristic:
A. Nausea, vomiting
B. Ulcers in tongue
C. Face edema
D. Dysgeusia
E. Paresthesias in extremities

66. The basic amount of iron in human organism is absorbed in
A. Stomach
B. Descending department of colon
C. Duodenum and small intestine
D. Ileum
E. Rectum

67. Iron is absorbed best of all
A. in a form of ferritin
B. in form hemosyderin
C. in the form of hem
D. as free trivalent iron
E. as free bivalent iron.

68. During a day iron can be absorbed in amount not more than
A. 0.5-1.0 mg
B. 1,5-2.5 mg
C. 4.0-4.5 mg
D. 10.0-12.0 mg
E. 15 mg

69. The reason of iron deficiency anemia in women there can be all mentioned, except for:
A. Abundant and protracted menstrual blood loss
B. Rendu-Osler-Weber's disease
C. Hemorrhoids
D. Tumours of gastrointestinal tract
E. Chronic cholecystitis

70. The most frequent reason of iron deficiency anemia in men is:
A. Bleeding from a gastrointestinal tract
B. Glomus tumours of kidneys
C. Alcoholic hepatitis
D. Hematuria form of glomerulonephritis
E. Chronic gastritis

71. Iron drugs are all listed, except for:
A. Tardiferon
B. Teraflex
C. Ranferon
D. Fenuls
E. Actiferrin

72. Basic principles of treatment of iron deficiency anemia are
A. Timely transfusion of whole blood
B. Prescription of the protracted and exact preparations of iron intravenously
C. Liquidations of reason of iron deficiency

D. Setting of preparations of iron intramuscular
E. Setting of rich in iron diet

73. It is worth to appoint treatment in deficit of iron:
A. Preparations of iron intravenously in connection with a meat diet
B. Preparations of iron intravenously in connection with the vitamins of group b intramuscularly
C. Regular transfusion of erythromass in connection with rich in fruit diet
D. Preparations of iron per os on the protracted term
E. None of mentioned

74. Correct recommendations for treatment of iron deficiency anemia are:
A. Vegetarian diet with sufficiency of apples, pomegranates, nuts
B. A necessity of the daily reception of caviar, meat, birds, white fish
C. Daily use in a meal 300 g of beef liver
D. Long-term reception of preparations of iron orally
E. None of mentioned

75. Iron drug is:
A. Contrical
B. Cyanocobalamin
C. Ranferon
D. Pyracetam
E. Teraflex

76. It is worth to appoint for treatment of deficit of iron
A. Preparations of iron intravenously and a meat diet
B. Preparations of iron intravenously
C. Preparations of iron intravenously and vitamins of group b i/m
D. Regular transfusion of erythromass and fruit diet
E. Preparations of iron orally on the protracted term

77. For iron deficiency anemia is characteristic:
A. hypochromia, microcytosis, syderoblasts in sternal punctate
B. hypochromia, microcytosis, target-like RBC
C. hypochromia, microcytosis, increase total iron binding capacity
D. hypochromia, microcytosis, decline total iron binding capacity
E. hypochromia, microcytosis, positive desferal test

78. Signs of syderopenic syndrome are all listed, except for:
A. angular stomatitis
B. glossitis
C. dryness and shedding hair
D. esophagitis
E. secretory insufficiency of stomach

79. What factor needs for absorption of B12-vitamin?
A. muriatic acid
B. gastrin
C. gastromucoprotein (intrinsic factor)
D. pepsin
E. folate acid

80. Whatever sign does not correspond to diagnosis of iron deficiency anemia?
A. colour index - 0,7
B. hypochromia of RBC
C. microcytosis
D. anizo-poykilocytosis
E. hypersegmentation of nuclei of neutrophills

81. Woman of 42 with a fibromyoma of uterus presented menorrhagic anemia: Hb - 80 g/L, hypochromia and microcytosis of RBC. What is the most probable diagnosis?
A. B-12-deficiency anemia
B. Folate-deficiency anemia

C. Aplastic anemia
D. Inherited spherocytosis
E. Iron deficiency anemia

82. The18 y. o. patient complains of a weakness, fatigue. Menstruations from 12, abundant, for 5-6 days. Skin is pale. In blood: Hb - 85 g/L, RBC - 3,8*10^12/l, CI - 0,67, serum iron - 4 mcmol/l, leuc. – 6*10^9/l, formula without features. What drug do you administer?

A. Erythromass
B. Cyanocobalamin
C. Ranferon
D. Pyridoxine
E. Folate acid

83. Mark the clinical sings of syderopenic syndrome:

A. angular stomatitis
B. parosmia and parageusia
C. esophagitis
D. all listed
E. nothing of marked

84. The reason of iron deficiency anemia in women there may be all listed, except for:

A. Abundant and protracted menstrual bleedings
B. Duodenal ulcer
C. Haemorrhoids
D. Tumors of gastrointestinal tract
E. Chronic biliary-dependent pancreatitis

85. The reason of iron deficiency anemia in men there may be all listed, except for:

A. Bleeding from duodenal ulcer
B. Irritable bowel syndrome
C. Haemorrhoids
D. Resection of stomach
E. Esophageal varicose veins dilatation at cirrhosis of liver

86. Basic principles of treatment of iron deficiency anemia are:

A. timely whole blood transfusion
B. prescription of the protracted and exact preparations of iron intravenously
C. liquidations of source of bleeding and setting of preparations of iron orally on the protracted term
D. setting of preparations of iron orally
E. all listed.

87. Anemia is considered to be hypochromous, when a colour index is:

A. 0.75
B. 0.85
C. 0,9
D. 1,0
E. 1,1

88. What index of peripheral blood does allow to estimate regenerator ability of bone marrow?

A. Erythrocariocytes
B. Megacariocytes
C. Reticulocytes
D. Erythrocytes
E. Leucocytes

89. For the estimation of supplies of iron at a hemosiderosis utilize:

A. Count of reticulocytes
B. Colour index of RBC
C. Myelogram
D. Determination of serum iron level and desferal test
E. All listed

90. The reason of B12-deficiency anemia can be:
A. Bleeding
B. Violations of synthesis of hemoglobin
C. Enhanced hemolysis
D. Increase level gastromucoprotein
E. All listed

91. What laboratory index is characteristic for B12-deficiency anemia?
A. Decline of color index
B. Increase serum iron level
C. Megaloblastic type of hemopoesis
D. Positive saccharose test
E. Decline of osmotic resistance of RBC

92. To the regenerator forms of erythrocytes belong:
A. Poycilocytes
B. Polychromatophylls
C. Anisocytes
D. Reticulocytes
E. Erythroblasts

93. The life cycle of erythrocytes is:
A. 7 days
B. 50 days
C. 70 days
D. 75 days
E. 120 days

94. What is the principal reason of microspherocytosis?
A. Parafunction of hemoglobin
B. Antibodies
C. Defect of structure of protein in membrane of RBC
D. Infection
E. Intoxication

95. The systemic increase of lymphonodes is characteristic for:
A. Hypoplastic anemia
B. Myeloma
C. Rendu-Osler-Weber's disease
D. Addison-Biermer anemia
E. Chronic lympholeukemia

96. At what diseases does the expressed absolute lymphocytosis take a place?
A. Lymphogranulomatosis
B. Chronic lympholeukemia
C. Lymphosarcoma
D. Tuberculosis of lymphatic nodes
E. Myeloma

97. A morphological diagnosis of lymphogranulomatosis is reliable at presence in histological lymphonodus preparation of:
A. Pirogov-Lanhgans cells
B. Prolymphocytes
C. Lymphoblasts
D. Reed-Sternberg cells
E. Mononuclears

98. What factor is a clotting factor of coagulation?
A. Thrombocytes
B. Heparin
C. Plasminogen
D. Fibrinogen

E. Serotonin

99. In the second phase of coagulation takes place:

A. Formation of thromboplastin
B. Formation of fibrin
C. Aggregation of thrombocytes
D. Thrombin formation
E. Retraction of blood clot

100. Deficiency in what factor leads to hemophilia B?

A. VIII
B. IX
C. X
D. XI
E. V

101. Take initial diagnosis patient with iron serum level 3-7 mcmol/l.

A. Thalassemia
B. Iron deficiency anemia
C. Hemolytic anemia
D. Chronic disease anemia
E. Syndrome of parasitic invasion

102. The clinical picture of iron deficiency is characterized by development of:

A. Syderopenic syndrome
B. Arthral syndrome
C. Hemorragic syndrome
D. Heart failure
E. Arterial hypertension syndrome

103. What index does allow suspecting iron deficiency anemia?

A. Hypochromia of RBC
B. Granulocytopenia
C. Microspherocytosis
D. Macrocytosis
E. Decline of hematocrit

104. What signs are characteristic the syderopenic syndrome?

A. Glossitis
B. Angular stomatitis
C. Koilonychia
D. All listed
E. Esophagitis

105. A patient of 57 at inspection found out the developed osteoporosis of vertebrae. In a blood test: RBC-3.4*10^12/l, Hb-108 g/L, leucocytes-5,6*10^9/l. lymphocytes-27%, b-7%, s-58%, monocytes-8%, thrombocytes-145*10^9/l, ESR-55 mm/h. Total protein - 264 g/l. What should be done for verification of diagnosis of myeloma?

A. Sternal punction
B. ECG
C. Chest X-ray
D. Fibrogastroscopy
E. Lumbal punction

106. Patient of 27 y.o. Fell ill acutely: the temperature of body rose to 39 C, there was driving sweat, chill; in 2 weeks under act of antibiotics and antipyretics a temperature went down to 37,8-38,40oC, sweating remained. The doctor found out the increased neck lymphatic nodes (on the left) of dense consistency, hyperemia and increase of tonsils, and also easy systolic noise on an apex and basis of heart. Blood test: hemoglobin - 95 g/l, erythrocytes 3,2xtera/l, colour index 0,9; leucocytes of 12,5x10^9/l (bas - 2, eos - 6, band - 10, segment. - 64, lymphocytes - 8, m - 10). ESR - 60 mm/h. What is diagnosis?

Lymphogranulomatosis
Bacterial endocarditis

Acute leukemia
Sepsis
Reactive lymphadenitis

107. Patient of 24 without complaints. During the planned prophylactic inspection on the chest X-ray found out the increase of shade of mediastinum and conglomerate of lymphatic nodes of radix of left lungs. Peripheral lymphatic nodes are not increased. In biopsy material, got by transthoracic punction from the lymphatic nodes of mediastinum - Berezovsky-Shterhberg cells. What is diagnosis?

A. Lymphogranulomatosis
B. Besnier-Boeck-Schaumann disease
C. Tuberculosis of mediastinal lymphatic nodes
D. A cancer of lungs
E. Chronic lymphadenitis

108. A patient, 65 years old, complaints about permanent pain in the back (in the projection of pectoral department of spine), loss of weight, weakness. On the X-ray of the proper area of spine is a decline of height of body of Th 7. On the roentgenogram of bones of skull are plural lytic points. In an urine analysis - Ben-Jones protein. In material of sternal punctate - 15% plasmatic cells. Serum calcium level - 3,2 mmol/L . What is diagnosis?

A. Multiply myeloma
B. Cancer with metastases to the bones
C. Lymphogranulomatosis
D. Osteoporosis
E. Osteomyelitis

109. Platelet component of hemostasis is characterized by:

A. Protrombin level
B. Autocoagulational test
C. Coagulation time by lee-white
D. Activated tromboplastin time
E. Bleeding time by Duke

110. What anemia is characteristic for decrease serum iron level?

A. Hypoplastic
B. Megaloblastic
C. Minkowsky-Shauffard
D. Iron deficiency
E. Thalassemia

111. Blast cells appear in peripheral blood in patients with:

A. B12-folate-deficiency anemia
B. Hemolytic anemia
C. Aplastic anemia
D. Acute leukemia
E. Werlhof's disease

112. Hematocrit rises in patients with:

A. Acute leukemia
B. Erythremia
C. Chronic myeloleukemia
D. Myeloma
E. Chronic lympholeukemia

113. Name the basic morphological sign of Minkowsky-Shauffard disease:

A. Clasmocytoma
B. Drepanocytosis
C. Microspherocytosis
D. Microcytosis
E. Macrocytosis

114. What laboratory index does allow take diagnosis of autoimmune hemolytic anemia?

A. Saccharose's test
B. Coombs' test
C. Autohaemolytic test
D. Determination of osmotic RBC resistance
E. Bleeding time

115.What anemia is an enhanced contain in blood of fetal hemoglobin at?
A. Microspherocytosis
B. B12-folate-deficiency anemia
C. Aplastic anemia
D. Thalassemia
E. Autoimmune hemolytic anemia

116. What medication is basic in treatment of Hemophilia A?
A. Fibrinogen
B. Hemostatic sponge
C. Cryoprecipitate
D. Frozed plasma
E. Erythromass

117. What drugs are basic in conservative therapy of idiopathic thrombocytopenic purpura?

A. Hemotransfusion
B. Heparin
C. Cryoprecipitate
D. Glucocorticoids
E. Dicinon

118. Patient of 24, was directed on consultation to the hematologist concerning a repeated icterus, splenomegaly. Blood test: RBC - 3.1 tera/L, Hb - 108 g/L, CI - 1.0, reticul. - 15%, diameter of RBC- 5.0 mcm, gen. bilirubin - 65 mcmol/L, undirect - 60 mcmol/L, direct - 5.0 mcmol/L. Sterkobilin level increased in faeces, urine. Your initial diagnosis:
A. Minkowsky-Shauffard anemia
B. Gilbert's disease
C. Addison-Biermer anemia
D. Thalassemia
E. Marchiafava-Micheli disease

119. A girl of 15 years old - an internist diagnosed an anemic syndrome which arose up as a result polymenorrhoea during a year and exception from the feed of meat meals. General state is moderate. Blood test: RBC - 1,8 tera/L, Hb - 62 g/L, CI - 0,87, leuc. - 3,8 giga/L, tr. - 160 giga/L, ESR - 26 mm/h. Serum iron level - 6.8 mcmol/L. What medical tactic should be in this case?
A. Reception of iron drugs orally
B. Transfusion of erythromass
C. A reception of iron parenteral drugs
D. Application of preparations of human erythropoetin
E. All listed

120. 68-years-old patient has IHD, the attacks of retrosternal pain became more frequent, a requirement was increased in nitroglycerine, the dyspnea appeared at the insignificant physical exertion. ECG is without dynamics. Blood test: RBC - 2,4 tera/L, Hb - 70 g/L, CI - 1.2, leuc. - 3,8 giga/L, tr. - 130 giga/L, ESR - 26 mm/h. A patient refuses the bone marrow examination. What drug should be administered in this case?
A. Vitamin B12 i/m
B. Iron drugs orally
C. Increase of daily dose of nitrates
D. Transfusion of erythromass
E. All invalid

121. The patient, 50 years old, complains of a general weakness, dizziness, heaviness in the upper half of abdomen, paresthesia of finger-tips upper and lower extremities. Objectively: a skin is icteric, tongue of

raspberry color, smooth and shiny, Hepatomegaly. Blood count: Hb - 90 g/L, RBC - 2,3 tera/L, retic. - 0,2%, CI -1,2, macrocytosis; Zholli bodies, Kebot rings. What is tactic of treatment?
A. Vitamin B12 i/m
B. Desferal i/m
C. Blood transfusion
D. Iron drugs orally
E. Prednisolone orally

122. A woman notes a general and muscular weakness, dyspnea, and dizziness, fragility of hairs and nails, desire to eat a chalk. In anamnesis is fibromioma uterus. Blood test: RBC 2,8*10^12/l, hemoglobin 105 g/L, colour index 0,78, anisocytosis. What additional research will help verification a diagnosis?
A. Serum iron level
B. B12 serum level
C. Osmotic resistance of RBC
D. Coagulogram
E. Proteinogram

123. A patient complains of the loss of appetite, sense of heaviness in epigastria, diarrhea. A skin is pale icteric, tongue of raspberry color, smooth, brilliant, at palpation pain in epigastrium. Blood test: RBC 2,5*tera/L, Hb-96 g/L, C.I. 1,2, L. 2,9*10^9/L, ESR-30 of mm/h, there are Zholli corpuscules, Kebot rings. What drug does it follow to begin treatment from?
A. Cyanokobalamin
B. Ranferon
C. Prednisolone
D. Venofer
E. Heparin

124. Patient of 39, complaints of periodic dizziness, enhanced fatigue. Objectively: skin and visible mucus pale. Ps - 100 per min. BP is 85/45 mm hg. Cor - tones are rhythmic, sinus tachycardia. Blood count: RBC - 2,2 *10^12/L, Hb - 90 g/L, serum iron level - 7 mcmol/l, total binding iron capacity - 42,6 mcmol/L. What drugs does it follow to begin treatment from?
A. Iron drugs orally
B. Iron drugs i/v, i/m
C. Aminicapronic acid, dicinon, vikasol
D. Transfusion of erythromass
E. Transfusion of fresh-frozen plasma

125. Patient of 27 complains of dizziness, weakness of muscles, nausea, decline of appetite, dryness of skin, fragility of nails and hair. She is ill half a year (after birth of child). Objectively: a skin and mucosa is pale. P-80/min, rhythmic. Tones of heart are muted, systolic murmur on the apex of heart. A stomach is soft, painless at palpation. Blood count: Hb-80g/L; RBC-2,6 tera/L, CI-0,8. Anisocytosis, poykilocytosis: reticulocytes - 1%. Serum iron level - 6,8 mcmol/L. What treatment should be administer the patient?
A. Iron drugs orally
B. Blood transfusion
C. Folic acid orally
D. Iron drugs i/v, i/m
E. Cyanokobalamin i/m

126. A 40-years-old woman suffers from menorrhagias complains of twinkling of "flies" before eyes, dizziness, dryness of skin, shedding of hair. At inspection: pallor skin and mucosa. Ps-100 per min, rhythmic and tones on an apex are increased, systolic murmur above all of points of heart. Hb-90 g/L, RBC-3,3*10^12/L, CI-0,7, leuc.-3,1*10^9/L, eos-2%, band-3%, s-70%, l-25%, m-10%, hypochromia, anisocytosis, microcytosis, serum iron level -7,2 mcmol/L. What is the prophylaxis of this disease?
A. Iron drugs orally
B. Enough diet
C. Cyankobalamin
D. Hemotransfusion
E. Polivitamins

127. A 40-years-old woman suffers from menorrhagias complains of twinkling of "flies" before eyes, dizziness, dryness of skin, shedding of hair. At inspection: pallor skin and mucosa. Ps-100 per min, rhythmic and tones on an apex are increased, systolic murmur above all of points of heart. Hb-90 g/L, RBC-3,3*10^12/L, CI-0,7, leuc.-3,1*10^9/L, eos-2%, band-3%, s-70%, l-25%, m-10%, hypochromia, anisocytosis, microcytosis, serum iron level -7,2 mcmol/L. What is diagnosis?

A. Iron deficiency anemia
B. B12-folate deficiency anemia
C. Acute posthemorrhagic anemia
D. Aplastic anemia
E. Hemolytic anemia

128. Patient of 44 y.o. complains of a general weakness, palpitation, dyspnea at the physical exertion. “Ulcerous” anamnesis - 20 years. Objectively: RR- 19/min, pulse – 100/min, BP 110/70 mm hg. A skin is pale, dry. Nails not shining, serrated, with transversal strings, hair is easily spoiled. Angular stomatitis. Cardiac tones are muffled, systolic murmur above the apex of heart. Blood count: RBC - 3,9 • tera/L, Hb - 90 g/L, ret - 0,8%; leuc - 4,2 • 109/L; e - 1%; band. - 1%; s - 53%; lymphocytes - 36%; m- 9%; ESR - 20 mm/h. What anemia is developed in this patient?

A. Iron deficiency
B. Acute posthemorrhagic anemia
C. B12-deficiency
D. Folate deficiency
E. Hemolytic

129. Patient, 58 years old - complains of a weakness, severe fatigue, palpitation, dizziness, numbness of extremities and “ants”. During many years is ill chronic gastritis. Objectively: skin pale, easy jaundice; atrophy of papillae of language. Cardiac tones are muffled, systolic murmur above the apex of heart. Blood count: RBC - 1,6 • tera/L, Hb - 64 g/L; thrombocytes - 48 • 10^9g/L; leucocytes -3 • 10^9/L; eos. - 1%; band. - 1%; segment. - 39%; l- 52%; m - 8%; ESR - 20 mm/h, macrocytosis. What anemia did develop in patient?

A. B12-deficiency
B. Acute posthemorrhagic anemia
C. Iron deficiency
D. Folate deficiency
E. Hemolytic

130. There are thrombopenia in peripheral blood and higher content of megacaryocytes at bone marrow biopsy. What is the most probable diagnosis?

A. Aplastic anemia.
B. Acute leukemia.
C. Chronic lymphatic leukemia.
D. Idiopathic thrombocytopenic purpura.
E. Chronic hepatitis.

131. The complete blood count test : Er. - 1,3*10 12/l, Hb 58 g/l, CI - 1,3, megaloblasts 2 on 100, reticulocytes 0,2%, Leucocytes - 2,8 109/l, Eos. 1%, Youn. 1%, Band cel. 8%, Segm. 45%, Lymph. 40%, Mon. 5%, platelets 10*104/l, ESR 30 mm/hour, anisocytosis, poikilocytosis, macrocytosis. What is diagnosis?

A. Iron-deficiency anemia.
B. B-12 deficiency anemia.
C. Aplastic anemia.
D. Acute leukemia.
E. Agranulocytosis.

132. The complete blood count test: Er 3,5*10 12/l, Hb 110 g/l, Leucocytes - 2,3 109/l, Basoph. 5,5%, Eos. 9%, Promyelocytes 2%, myelocytes 22%, metamyelocyte 20,5%, Band cel.15%, Segm.12%, Lymph. 8,5%, Mon. 5,5%, platelets of 3,8*104/l, ESR 20 mm/hour. What is diagnosis?

A. Acute leucosis.

B. Chronic lymphatic leukemia.
C. Myelosis.
D. Erithremia.
E. Multiple myeloma.

133. Patient C., 23 years, was admitted to the hospital. He had quinsy and noted the increase of lymph nodes, high temperature was saved. The complete blood count test: Er 4,1* 10 12/l, Hb 130 g/l, platelets 23*104/l, Leucocytes 2,5*109/l, lymphomonocyte 45%, ESR 35 mm/hour. There are clinical signs of quinsy and hepatomegalia at examination. What is diagnosis?
A. Hodgkin's lymphoma.
B. Infectious mononucleosis.
C. Chronic lymphatic leukemia.
D. Acute hepatitis.
E. Acute monoblastic leukemia.

134. Patient C., 23 years, was admitted to the hospital. He had quinsy and noted the increase of lymph nodes, high temperature was saved. The complete blood count test: Er 4,1* 10 12/l, Hb 130 g/l, platelets 23*104/l, Leucocytes 2,5*109/l, lymphomonocyte 45%, ESR 35 mm/hour. There are clinical signs of quinsy and hepatomegalia at examination. What additional investigations need to confirm a diagnosis?
A. Bone marrow examination.
B. Lymph node biopsy .
C. Ultrasound examination of liver and spleen.
D. Throat swab.
E. Chest X-ray .

135. The complete blood count test: Er. - 1,3*10 12/l, Hb 58 g/l, CI - 1,3, megaloblasts 2 on 100, reticulocytes 0,2%, Leucocytes - 2,8 109/l, Eos. 1%, Youn. 1%, Band cel. 8%, Segm. 45%, Lymph. 40%, Mon. 5%, platelets 10*104/l, ESR 30 mm/hour, anisocytosis, poikilocytosis, macrocytosis. What additional investigations need to confirm a diagnosis?
A. Bone marrow examination.
B. Ultrasound examination of liver and spleen.
C. Chest X-ray.
D. Vitamin B-12 level test.
E. Iron level test.

136. The complete blood count test: Er. 2,8*10 12/l,, Hb of 80 g/l, CI 0,8, reticulocytes 20%, Leucocytes 7,5*109/l, Eos.2%, Band cel. 4%, Segm. 54%, Lymph.37%, Mon. 3%, platelets 2,0 *104/l, ESR 15 mm/hour, microspherocytosis. What additional investigations need to confirm a diagnosis?
A. Bone marrow examination.
B. Vitamin B-12 level test
C. Iron level test.
D. Ultrasound examination of liver and spleen.
E. Measurement of osmotic resistance of erythtrocytes.

137. The complete blood count test: Er. 2,8*10 12/l, Hb of 80 g/l, CI 0,8, reticulocytes 20%, Leucocytes 7,5*109/l, Eos.2%, Band cel. 4%, Segm. 54%, Lymph.37%, Mon. 3%, platelets 2,0 *104/l, ESR 15 mm/hour, microspherocytosis. What is diagnosis?
A. B-12 deficiency anemia.
B. Folate deficiency anemia.
C. Congenital hemolytic anemia.
D. Iron-deficiency anemia.
E. Acute leukemia.

138. Female, 72 years, complain of weakness, aversion to meat food, loss in weight on 12 kg in the half a year. Objective state: skin is pale and mild icteric; enlarged, not mobile, compact lymph node is palpated above a collar-bone at the left. A liver enlarged on 4 sm, compact, mild tenderness. The complete blood count test: Er. 2,5*10 12/l, Hb of 78 g/l, platelets of 460*109/l, Leucocytes 3,8*109/l, a leucocytes formula is normal, ESR 55 mm/hour. What is the most probable diagnosis ?

A. Acute leukemia.
B. B-12 deficiency anemia.
C. Folate deficiency anemia.
D. Stomach cancer with metastases.
E. Multiple myeloma.

139. Female, 72 years, complains of weakness, aversion to meat food, loss in weight on 12 kg in the half a year. Objective state: skin is pale and mild icteric; enlarged, not mobile, compact lymph node is palpated above a collar-bone at the left. A liver enlarged on 4 sm, compact, mild tenderness. The complete blood count test: Er. 2,5*10 12/l, Hb of 78 g/l, platelets of 460*109/l, Leucocytes 3,8*109/l, a leucocytes formula is normal, ESR 55 mm/hour. What additional investigations need to confirm a diagnosis?

A. Bone marrow examination.
B. Ultrasound examination of liver and spleen.
C. Lymph node biopsy .
D. Esophagogastroduodenoscopy
E. pH-metry.

140. Patient, 57 years, complains on epigastric pain after meal, liquid stool, high temperature 37,5 Co, feeling of numbness and pricking in extremities, weakness. He had resection of stomach on account of peptic ulcer and epigastric pain, diarrhea, anemia are appeared in 4 years. Objective state: skin is pale and mild icteric. There are tachycardia and mild systolic murmur in cardiac apex and in 5 point. A liver enlarged on 3 sm, spleen on 2 sm. The complete blood count test: Er.-2,3*10 12/l, Hb- of 80 g/l, CI-1,2, L-2,3*109/l, a leucocytes formula is normal, platelets 140*103/l, ESR-45 mm/hour. Macrocytosis. What is the most probable diagnosis ?

A. Iron-deficiency anemia.
B. Stomach cancer .
C. B-12 deficiency anemia.
D. Congenital hemolytic anemia.
E. Folate deficiency anemia.

141. Patient, 57 years, complains on epigastric pain after meal, liquid stool, high temperature 37,5 Co, feeling of numbness and pricking in extremities, weakness. He had resection of stomach on account of peptic ulcer and epigastric pain, diarrhea, anemia are appeared in 4 years. Objective state: skin is pale and mild icteric. He has tachycardia and mild systolic murmur in cardiac apex and in 5 point. A liver enlarged on 3 sm, spleen on 2 sm. The complete blood count test: Er.-2,3*10 12/l, Hb- of 80 g/l, CI-1,2, L-2,3*109/l, a leucocytes formula is normal, platelets 140*103/l, ESR-45 mm/hour. Macrocytosis. What additional investigations need to confirm a diagnosis?

A. Ultrasound examination of liver and spleen.
B. Bone marrow examination.
C. Esophagogastroduodenoscopy
D. Measurement of bilirubin level.
E. Stomach X-ray .

142. Congenital hemolytic anemia is characterized by all listed signs, except for

A. Congenital cranium malformations.
B. At the beginning in childhood.
C. Decrease of osmotic resistance of leucocytes.
D. Positive Kumbs' test.
E. Enlarged spleen.

143. Patient was admitted to the hospital with epagastric pains. The state is heavy. Pale. Temperature – 38Co. He has gingivitis, petechiae, ossalgia. What investigation need first of all?
A. Measurement of leucocytes
F. Esophagogastroduodenoscopy
A. Diagnostic laparotomy
B. Measurement of hemoglobin level and erythtrocytes.
C. Platelets count.

144. A patient with haemophilia A, 18 years, is observed by haematologist. After fall from a horizontal bar knee-joint and elbow joints hemarthrosis are appeared. He was admitted to the haematological department of regional hospital. At examination: bleeding time by Dyuke – 4 minutes, activated partial thromboplastin time– 1 minute. What medicine is the most required in this situation?
A. Administration of recombinant clotting factor VIII
B. Fresh-frozen plasma
C. Cryoprecipitate
D. Platelets mass
E. Platelets concentrate

145. Male, 24 years, complains of the conglomerate of not matted together compact, painless lymph nodes 4-5 sm in diameter in the right supraclavicular area, high temperature to 39 Co periodically, skin itch and ostealgias in pelvis and thorax. The complete blood count test: Hb-95 g/l, L-12*109/l, Eos. –10%, ESR -35 mm/hour. X-ray chest: increase of mediastinal lymph nodes. Your tactic is?
A. Lymph nodes biopsy
B. Observation
C. Antibiotikotherapy
D. Physiotherapy.
E. Operation – neck lymphadenectomy

146. Female 26 years complains of appearance of not matted together compact lymph nodes 2-4 sm in a diameter in neck area on the left and in the right supraclavicular area, high temperature to 39 Co, skin itch, profuse nightly sweat, loss in weight on 10 kg in the last month. Lymph nodes biopsy: Berezovsky - Shternberg's cells. Your diagnosis is
A. Hodgkin's lymphoma.
B. Lymph nodes tuberculosis .
C. Chronic leukemia.
D. Metastases in neck and supraclavicular lymph nodes
E. Lymphosarcoma.

147. Patient, 48 years, stupor. To hear from complained of increasing weakness, fatigueability in last several days. He is pale, sweating all over. Pulse 126 per minute, BP 60/40 mm merc. At deep abdominal palpation: tenderness in right upper quadrant. A liver enlarged on 2 sm. Examination per rectum – melena. Patient excreted about 100 ml of urine in the last day. Blood test: Er. 1,8*1012/l, hemoglobin 52 g/l, hematocrit 22%. Prescribe urgent interventions.
A. Liver biopsy.
B. Observation
C. Transfusion of erythrocytes mass
D. Antibiotikotherapy.
E. Physiotherapy.

148. Patient, 28 years, had acute respiratory disease last month, took sulfonamides. During the week he suffer from sore throat at swallowing, high temperature to 39°C. He is pale, language is dry. There are plural ulcers with grey spot on the mucous of gums, soft and hard palate, tonsils. There are plural haematomas on the skin of shoulders, shins. Pulse 106 per min. BP 105/60 mm merc. The complete blood count test: Er.-

3.2*1012/l, Hb-104 g/l, CI-0.9, L-86.0*109/l, segm.-20%, мон.-5%, blast cells-75%. ESR 62 mm/hour. Platelets- 40 *109/l. Your initial diagnosis is

A. Acute leukemia.
B. Vensan's quinsy
C. Diphtheria
D. Medical allergy
E. Sepsis

149. The patient, 32 years, complains of weakness, general sweating, skin itch, high temperature, appearance of compact conglomerate on the neck at the left by the size of 2,0 * 1,5 sm, and also in the left axillary region. He is pale, lymph nodes are compact, painless, not matted together. A liver and spleen is not enlarged. The complete blood count test: Er. 3,3 *1012/l, Hb 90 g/l, CI 0,9. L - 14,5 *109/L, bas.-2%, eos.-6%, band cel.-10%, segm.-62%, lymph.-8%, mon.-12%. ESR 55 mm/hour. Platelets 360*109/l. Your initial diagnosis is

A. Hodgkin's lymphoma.
B. Lymph nodes tuberculosis
C. Lymphadenoma
D. Chronic leukemia.
E. Metastases in neck and axillary lymph nodes

150. Patient, 29 years. During the week he suffer from sore throat at swallowing, high temperature to 39°C, headache. He is pale, language is dry. There are plural ulcers with grey spot on the mucous of gums, soft and hard palate, tonsils. Pulse 110 in min. BP 110/60 mm merc. The complete blood count test: Er. 3,2 *1012/l, Hb of 100 g/l, CI 0,9. L - 80,0 *109/l, segm.-22%, mon.-3%, blast cells-75%. ESR 65 mm/hour. Platelets 42 *109/l. What investigations need to confirm a diagnosis?

A. Bone marrow examination.
B. Syphilis test
C. Analysis of blood sterility
D. Throat swab to identify diphtheria
E. Throat swab to identify atipical cells and BC

151. The patient, 30 years, complains of weakness, general sweating, skin itch, high temperature, appearance of compact conglomerate on the neck at the left and in the left axillary region by the size to 2,0 sm. He is pale, lymph nodes are compact, painless, not matted together. A liver and spleen is not enlarged. The complete blood count test: Er.-3.2*1012/l, Hb-95 g/l, CI-0.9, L-12,5*109/l, bas.-2%, eos.-6%, band cel.--10%, segm.-64%, lymph.-8%, mon.-10%. ESR 60 mm/hour. Platelets 380 *109/l. What investigations need to confirm a diagnosis?

A. Lymph nodes biopsy
B. Liver-biopsy.
C. Observation
D. Analysis of blood sterility
E. Esophagogastroduodenoscopy

152. Patient, 48 years. He complains of the increase of neck lymph nodes, high temperature to 37,6. He began to ache 3 months ago. Objective state: painless, pasty, mobile lymph nodes are palpated on the right and on the left on the neck. Skin above lymph nodes is normal, pulse 72 per min., rhythmic. A liver and spleen is not enlarged. The complete blood count test: Er. 2,2*1012/l, Hb 72 g/l, CI 0,9. Platelets 100*109/l, leucocytes of 80*109/l, eos. 0, band cel. 4%, segm. 6%, lymph. 90%, mon. 0, ESR 10 mm/hour. What is the most probable diagnosis ?

A. Chronic lymphatic leukemia
B. Hodgkin's lymphoma
C. Lymph nodes tuberculosis .
D. Lymphadenoma
E. Metastases in neck lymph nodes

153. In woman, 56 years, nosebleeds is stopped with difficulty during hypertension stroke. It is bigun again in 6 hours, ear bleeding, blood in the vomit, ecchymoses in the area of injections, oliguria and urine as "meat pigwashes" are appeared. Take a diagnosis.
A. Disseminated intravascular clotting-syndrome
B. Idiopathic thrombocytopenic purpura
C. Hemophilia
D. Randy-Osler's desease
E. Acute vascular purpura

154. Basic principles of treatment of iron-deficiency anemia are:
A. Timely blood transfusion
B. Prolonged and exact administration of iron drugs intravenously
C. Liquidation of reason of iron-deficiency
D. Prescription iron drugs per os for a long time
E. Liquidation of reason of iron-deficiency and prescription iron drugs per os for a long time

155. The reason of iron-deficiency anemia in men are all listed, except for
A. Gastrointestinal bleeding at duodenal ulcer
B. Irritable bowel syndrome
C. Haemorrhoids
D. Stomach resection
E. Esophageal varices at cirrhosis

156. The reason of iron-deficiency anemia in women are all listed, except for
A. Hypermenorrhea and polymenorrhea
B. Duodenal ulcer
C. Haemorrhoids
D. Gastrointestinal tumours
E. Chronic biliary-dependent pancreatitis

157. Name the clinical signs of sideropenic syndrome:
A. Angular stomatitis
B. dysgeusia and dysosmia
C. glossitis
D. all listed
E. nothing listed

158. Female, 18 years, complains of weakness, fatigueability. Gynecological anamnesis: mensesfrom 12 years, polymenorrhea, last 5-6 days. She is pale. The complete blood count test: Hb - 85 g/l, Er. 3,8 *106/l, CI - 0,67, iron level - 4 mcmol/l, leucocytes 6*109/l, leucocytes formula is normal. What medicine is the most required in this situation?
A. Erythrocytic mass
B. Vitamin B12
C. Ferroplex
D. Piridoxin
E. Ferrum

159. Woman, 42 years, with fibromioma uteri menorrhagies has anemia: Hb - 80 g/l, hypochromia and microcytosis. What is the most probable diagnosis ?
A. B12-deficiency anemia
B. Sickle cell anemia
C. Aplastic anemia
D. Hereditary spherocytosis

E. Iron-deficiency anemia

160. At patients with B12-deficiency anemia next symptom is observed more often
A. Numbness of extremities.
B. Deep sensitiveness violations.
C. Romberg's positive symptom
D. Muscular hypocinesia and rigidity
E. Pyramidal paraparesis.

161. Hemolytic anemia is characterized by next laboratory indexes
A. Increase transferring serum level .
B. Reticulocytosis.
C. Low erythropoietin level .
D. Hyperthrombocytosis.
E. Bleeding sickness.

162. What white blood cells don't granulocytes?
A. Band neutrophil.
B. Eosinophil.
C. Monocyte.
D. Basophile.
E. Segmental neutrophil.

163. The beginning of chronic lymphatic leukemia is characterized by next state
A. Anemia.
B. Lymphadenopathy.
C. Enlarged liver.
D. Splenomegaly.
E. Thrombocytopenia.

164. Hypersplenism is:
A. Enlarged spleen
B. Decrease only platelets in peripheral blood
C. Decrease only granulocytes in peripheral blood
D. Decrease platelets, granulocytes and erythrocytes in peripheral blood
E. Enlarged spleen, decrease only granulocytes in peripheral blood

165. In adults enlarged spleen in the beginning of disease is characteristic for
A. Hemolytic anemia
B. Iron-deficiency anemia
C. Chronic hepatitis
D. Enterocolitis
E. B12 deficiency anemia

166. What sign do not characteristic for iron-deficiency anemia?
A. Color index 0,7
B. Hypochromia
C. Microcytosis
D. Aniso-poikilocytosis
E. Hypersegmentation of neutrophils

167. The clinical signs of sideropenic syndrome are all listed, except for:
A. Angular stomatitis

B. Glossitis
C. Hair dryness and shedding
D. Esophagitis
E. Gastric secretory insufficiency

168. The iron-deficiency anemia is characteristic by:
A. Hypochromia, microcytosis, sideroblasts in bone marrow biopsy
B. Hypochromia, microcytosis, target erythrocytes
C. Hypochromia, microcytosis, increase iron-binding capaciti
D. Hypochromia, microcytosis, decrease iron-binding capaciti
E. Hypochromia, microcytosis, positive desferal test

169. You prescribe patient with iron-deficiency anemia
A. Iron drugs intravenously and meat diet
B. Iron drugs intravenously
C. Iron drugs and B-group vitamins intramuscular
D. regular blood transfusion and fruit diet
E. Iron drugs per os for a long time

170. Iron drugs are
A. Contrical
B. Phytinum
C. Globiron
D. Phesam
E. Glicesed

171. Pregnancy with iron-deficiency anemia needs
A. Iron drugs per os to births and all period of breast-feeding
B. Diet with red fish, pomegranates and carrot
C. Blood transfusion before births
D. Ferrumlek intravenously 10 times
E. Nothing listed

172. The basic quantity of iron is absorb
A. in rectum
B. in the descending part colon
C. in duodenal and jejunum
D. in ileum
E. all it is not true

173. Correct recommendations for iron-deficiency anemia treatment are
A. Vegetarian diet with plenty of apples, carrot, pomegranates, nuts
B. Obligatory daily caviar, meat, bird, white fish intake.
C. Daily 300 liver paste intake
D. Iron drugs per os for a long time
E. Nothing listed

174. You prescribe patient with iron-deficiency anemia
A. Iron drugs intravenously and meat diet
B. Iron drugs and B-group vitamins intramuscular
C. Regular blood transfusion and fruit diet
D. Iron drugs per os for a long time
E. Nothing listed

175. Basic principles of treatment of iron-deficiency anemia are:

A. Timely blood transfusion
B. Prolonged and exact administration of iron drugs intravenously
C. Prescription iron drugs per os for a long time
D. Prescription iron drugs intramuscular
E. Liquidation of reason of iron-deficiency
F. Rich iron diet

Appendix 1

1	*2*	*3*	*4*	*5*	*6*
№	Basic stages of lesson their functions and meaning	Educational purposes in the levels learning	Methods for monitoring and training	Materials methodological software: control, illustrative, instructive	Distributing time in minutes
	Preparatory stage				
1.	Organizational measures				3 min.
2.	Formulation of learning goals and motivation			P. Ii the «Educational purposes» P. And «Actuality of topic»	12 min
3.	Monitoring initial level of knowledge and skills:				20 min.
	- etiology of asthma	α=2	Individual oral interviews	A table is «Etiology BA»	
	- key links in the pathogenesis of asthma	α=2	Test control level II	Tests II level	
	- clinical classification of asthma	α=2	Individual oral interviews	Table "Classification of asthma"	
	- typical clinical manifestations of asthma	α=2	Typical situation tasks level II	Structural and logic scheme of asthma	
	- laboratory and instrumental diagnosis of asthma	α=2	Typical situation tasks level II	Situational typical task level II	
	- complications of asthma	α=2	Test control level II	Tests II level	
	- treatment of asthma	α=2	Typical situation tasks level II	Situational tasks II level, set drugs	

	The main stage.				
4.	Formation of skills and abilities.				115 min.
	1. Curation to patients with asthma, collect complaints, history of disease	α=3	Practical professional training	Patient	
	2. Conduct an objective examination of the patient, identify the main symptoms and syndromes of asthma	α=3	Practical professional training	Patient	
	3. Formulate and substantiate a preliminary diagnosis	α=3	Practical professional training	Case History The approximate card for formation of professional skills	
	4. Plan of laboratory and instrumental examination of the patient	α=3	Practical professional training	Case History The approximate card for formation of professional skills Case	
	5. Interpret the results of laboratory and instrumental studies	α=3	Practical professional training Test control level III	The approximate card for formation of professional skills	
	6. To differential diagnosis of clinical conditions, accompanied by breathlessness and cough	α=3	Practical professional training in dealing with atypical clinical situations	Situational atypical tasks level III Tests III level	
	7. Give recommendations for treatment and diet of the patient with asthma	α=3	Test control level III Practical professional training	Treatment sheet Situational atypical tasks and tests Level III	
	8. Plan of treatment of the patient with asthma given the stage of the disease and the presence of complications	α=3	Practical professional training in dealing with atypical clinical situations Test control level III	Algorithms for treatment of patients with asthma	
	9. Be able to provide first aid in emergency situations	α=3	Practical professional training in resolving atypical clinical situations	Situational atypical tasks level III Algorithms first aid	
	Final stage		Analysis of clinical work	Results of clinical work	
5.	Control and correction of professional skills and abilities.	α=3	Solving problems and atypical test level III	Situational atypical tasks and tests level III	25 min.
6.	Summing up the lessons.			The approximate card for independent work with literature	
7.	Homework (basic and additional literature on the topic)		Evaluation of clinical work		

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Basic.

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