Protocol 2
Special Pathophysiology

Anaemia

Introduction

Anaemia is a syndrome characterized by a **decreased concentration of haemoglobin (Hb), a reduced number of red blood cells (RBC), and a decreased haematocrit (Hct)** below the lower limit of reference values. As a result, **the blood's oxygen-carrying capacity is reduced**, leading to **tissue hypoxia** and the development of typical clinical manifestations.
The anaemic syndrome arises from a wide range of causes and develops through various mechanisms. Understanding the etiopathogenesis of individual forms of anaemia is therefore essential for correct diagnosis and for proper and effective treatment.

Classification of anaemias according to etiology

A. Disorders of erythrocyte production

Name of anaemia	*Cause*	*Mechanism*
Sideropenic	Iron deficiency	Impaired haem synthesis
Megaloblastic	Vitamin B12 or folic acid deficiency	Impaired DNA synthesis
Sideroblastic	Hereditary (ALA-synthetase deficiency) Acquired (heavy metal poisoning)	Impaired haem synthesis
Aplastic	Hereditary (Fanconi anaemia) Acquired (radiation, chemical agents) Myelodysplastic syndrome	Suppression of bone marrow haematopoiesis
Anaemia of chronic diseases	In chronic inflammation, infections, malignant diseases	Cytokines in chronic inflammation: • ↑ hepcidin production → ↓ Fe • Excessive IL-6 expression • Inhibition of erythropoiesis
	In chronic kidney disease	↓ erythropoietin, haemolysis, bone marrow suppression
	In hematopoietic malignancies and bone metastases	Bone marrow infiltration
	In chronic liver diseases	Lack of transferrin, ferritin Inflammatory cytokines
Sickle cell anaemia	Inherited mutation of the gene encoding the β-chain of HbA	Production of pathological HbS
Thalassemias	Hereditary	Impaired synthesis of the α- or β-chain of haemoglobin
Other	Protein deficiency	Lack of transferrin, ferritin, etc.
	Deficiency of vitamin B1, B6, C	Suppressed erythropoiesis, impaired hem synthesis, impaired Fe absorption

B. Increased loss of erythrocytes

Name of anaemia	*Cause*
Post-haemorrhagic	Acute blood loss (trauma, surgery, blood donation)
	Chronic blood loss (gastrointestinal bleeding – ulcers, tumours, haemorrhoids; gynaecological bleeding – menorrhagia, metrorrhagia)

C. Increased destruction of erythrocytes (haemolytic anaemias)

Name of anemia	*Cause*	*Example*
Corpuscular haemolytic (congenital, hereditary)	Membranopathies	Hereditary spherocytosis, hereditary eliptocytosis
	Enzymopathies	G6PD deficiency, pyruvate-kinase deficiency
	Haemoglobinopathies	Sickle cell anaemia, thalassemias
Extracorpuscular haemolytic (acquired)	Immune-mediated	Rh incompatibility, transfusion reactions, autoimmunity
	Mechanical damage	Valve defects, artificial heart valve
	Toxic damage	Lead poisoning, snake venom
	Infections	Malaria, babesiosis
	Acquired membrane disorders	Paroxyzmal nocturnal haemoglobinuria

D. Other

Name	*Cause*
Relative anaemia „false anaemia“ Anaemia spuria	Hemodilution • 3. trimester of gravidity • retention of fluids in cardiovascular and renal diseases Redistribution of erythrocytes • splenomegaly
Hidden anaemia	Hemoconcentration in dehydration or hypoproteinemia may mask anaemia

Clinical classification of anaemias

a. According to the time of onset (time course)

Name	*Example*
Acute	Acute bleeding due to injury, vessel rupture
Chronic	Chronic blood loss, chronic diseases, iron or vitamin deficiency

b. According to the size of erythrocytes (MCV)

Name	*Example*
Mikrocytic	Iron deficiency, disorders of haem or globin synthesis
Normocytic	Posthemorrhagic, haemolytic anaemia, anaemia of chronic diseases
Makrocytic	Megaloblastic anaemia

c. According to the haemoglobin content in erythrocytes (MCH)

Name	*Example*
Hypochromic	Iron deficiency, disorders of haem or globin synthesis
Normochromic	Posthemorrhagic, haemolytic anaemia
Hyperchromic	Megaloblastic anaemia

d. Based on the effective production of erythrocytes in the bone marrow

Name	*Example*
Aregenerative	Aplastic anaemia
Hyporegenerative	Iron deficiency anaemia
Regenerative	Posthemorrhagic, haemolytic anaemia

Clinical symptoms of anaemias

Clinical symptoms of anaemias are divided into general (nonspecific) and specific symptoms. Nonspecific symptoms occur in all types of anaemia and arise mainly due to reduced haemoglobin transport capacity and the development of compensatory mechanisms. Specific symptoms are characteristic only for certain types of anaemia and reflect the particular pathogenetic mechanisms involved in their development—such as manifestations of iron deficiency, generalized suppression of haematopoiesis, or increased breakdown of haem to bilirubin, etc.

General (nonspecific) symptoms

- Reduced oxygen transport – hypoxia
  - Dyspnoea, fatigue, weakness, dizziness, malaise, paleness
  - In patients with coronary artery disease – angina pectoris (substernal pain)
- Reduced plasma volume
  - Postural hypotension
- Increased cardiac output
  - Palpitations, murmurs, tachycardia

Specific Symptoms

- ***Iron-deficiency anaemia***
  - Koilonychia (nail deformities), brittle nails
  - Hair loss
  - Pica (eating non-food items such as ice, paper, etc.) – rare
  - Inflammation in the oral cavity
  - Swallowing disorders
  - Gastritis

- ***Haemolytic anaemia***
  - Jaundice
  - Splenomegaly
- ***Vitamin B12 deficiency***
  - Ataxia
  - Peripheral neuropathy – paresthesias
- ***Aplastic anaemia***
  - Thrombocytopenia – bleeding tendency, bruising
  - Leukopenia – increased frequency of infections

Basic haematological and biochemical parameters in anaemia diagnostics

Name	*Abbrev.*	*Reference values*	*Evaluation*
Haemoglobin (Hb)	HGB	men:130 - 175 g/l women:120 - 165 g/l	↓ - anaemia ↑ - polyglobulia
Red blood cell count	RBC	men: 4,2 - 5,8 x 10^{12}/l women:3,8 - 5,2 x 10^{12}/l	↓ - anaemia ↑ - polycythaemia
Haematocrit	HCT	men: 0,40 - 0,54 l/l women: 0,35 - 0,45 l/l	↓ - anaemia, haemodilution ↑ - polyglobulia, altitude sickness, haemoconcentration
Mean Corpuscular Volume	MCV	80 - 97 fl	↓ - microcytosis ↑ - macrocytosis
Mean Corpuscular Haemoglobin	MCH	27 - 32 pg	↓ - hypochromia ↑ - hyperchromia
Mean Corpuscular Haemoglobin Concentration	MCHC	320 - 370 g/l	↓ - hypochromia ↑ - hyperchromia
Red Cell Distribution Width	RDW	12 – 13,6 %	↑ - anisocytosis (heterogenity of erythrocytes)
Reticulocytes	RET	men: 0,5 – 2,5 % women:0,8 – 4,0 %	↑ - increased erythropoiesis ↓ - decreased erythropoiesis
White blood cell count	WBC	4 – 10 x 10^{9}/l	↓ - leucopenia ↑ - leucocytosis
Platelet count	PLT	140 – 420 x 10^{9}/l	↓ - thrombocytopenia ↑ - thrombocytosis
Serum iron	S-Fe	men: 14 – 28 μmol/l women: 12 – 23 μmol/l	↓ - iron deficiency ↑ - haemochromatosis, haemolytic anaemias
Total Iron-Binding Capacity	TIBC	44 - 80 μmol/l	↓ - liver diseases, infections, inflammation ↑ - iron deficiency
Transferrin	TRF	2,0 – 3,6 g/l	↓ - liver diseases, infections, inflammation ↑ - iron deficiency
Transferrin saturation	sat.TRF	15 – 45 %	↓ - sideropenia ↑ - haemochromatosis
Ferritin	FER	men: 30 – 400 μg/l women: 15 – 300 μg/l	↓ - iron deficiency ↑ - iron overload
Folic acid	FOLAT	12,19 – 54,35 nmol/l	↓ - megaloblastic anaemia
Vitamin B12	B12	156 – 672 pmol/l	↓ - megaloblastic anaemia, hyperhomocysteinaemia → cardiovascular risk
Erythrocyte sedimentation rate	FW	men: 2 - 5 mm/h women: 3 - 8 mm/h	↑ - anaemia ↓ - polyglobulia
Lactate dehydrogenase	LDH	< 8 μkat/l	↑ - haemolysis
Total bilirubin	S-BIL-T	5 – 21 μmol/l	↑ - haemolysis, liver diseases
Conjugated bilirubin	S-BIL-D	1 – 5 μmol/l	↑ - liver diseases
Unconjugated bilirubin	S-BIL-I	BIL-I = BIL-T – BIL-D	↑ - haemolysis

Case studies

Case Study 1

History: A 47-year-old administrative worker, reports progressively increasing fatigue, weakness, reduced performance during normal physical activity, and shortness of breath when climbing stairs, lasting about 6 months. In recent weeks, he has noticed pale skin and mild scleral icterus. No night sweats, bleeding, or infections. His diet is normal. He drinks 2–3 beers daily for the past 10 years. No known hereditary haematological diseases in the family history. No regular medication.

Physical examination:

Pale skin, mild scleral icterus, heart rate 92/min, hepatomegaly.

Laboratory findings:

HGB 96 g/L, HCT 0.3, MCV 94 fL, MCHC 310 g/L, RET 0.5%, S-Fe 38 µmol/L, FER 540 µg/L, TIBC 28 µmol/L, sat.TRF 80%, S-BIL 28 µmol/L, LDH mildly elevated, bone marrow aspiration: sideroblasts.

1. What changes are present in the haematological parameters?
2. What type of anaemia does the patient have (diagnosis)?
3. What is the etiopathogenesis of this anaemia?
4. Which enzyme is blocked in this disorder?
5. Describe the anaemia according to the morphological classification.

Case Study 2

History: A 32-year-old female teacher reports several months of fatigue, decreased concentration, palpitations during physical exertion, and frequent headaches. Recently, she has noticed increased hair loss, brittle nails, and dry skin. Her menstruation is regular but heavy (lasting 6–7 days, requiring pad changes every 2–3 hours). She is a vegetarian, consumes large amounts of coffee and tea, has no significant family history, and takes no medication.

Physical examination:

Pale skin and mucous membranes, dry and brittle hair, thin nails (koilonychia), tachycardia 100/min, normal blood pressure, no hepatosplenomegaly.

Laboratory findings:

HGB 92 g/L, HCT 0.29, MCV 72 fL, MCHC 290 g/L, S-Fe 5 µmol/L, RET 0.6%, FER 8 µg/L, TIBC 78 µmol/L, sat.TRF 6%, RDW increased.

1. What changes are present in the haematological parameters?
2. What type of anaemia does the patient have (diagnosis)?
3. What is the etiopathogenesis of this anaemia?
4. Describe the anaemia according to the morphological classification.

Case Study 3

History: A 58-year-old female accountant reports progressively worsening fatigue, pallor, palpitations, and dizziness. In recent months she has noticed burning of the tongue, loss of appetite, and tingling in the fingers and toes. No bleeding or infections. She eats a normal diet but has recurrent digestive problems and reports poor tolerance for meat. Family history is negative. Five years ago, autoimmune (atrophic) gastritis was diagnosed—confirmed by positive antibodies against parietal cells and intrinsic factor (IF).

Physical examination:

Pale skin with mild jaundice, smooth and red tongue (atrophic glossitis – “beefy red tongue”), pulse 88/min, balance disturbances and decreased sensation in the lower limbs (polyneuropathy), no hepatosplenomegaly.

Laboratory findings:

HGB 82 g/L, HCT 0.26, MCV 118 fL, MCHC 330 g/L, RET 0.3%, WBC 3.2 ×10⁹/L, PLT 110 ×10⁹/L, serum vitamin B12 85 pmol/L, folate normal, S-BIL-I 32 µmol/L.

Bone marrow: megaloblasts, hypersegmented neutrophils

Intrinsic factor antibodies: positive

1. What changes are present in the haematological parameters?
2. What type of anaemia does the patient have (diagnosis)?
3. What is the etiopathogenesis of this anaemia? Which blood cell lines are also affected?
4. What additional (non-haematological) symptoms occur in this type of anemia?
5. Describe the anaemia according to the morphological classification.

Case Study 4

History: A 26-year-old male technician reports progressively worsening fatigue, pallor, frequent dizziness, and palpitations during the past 2 months. He has also noticed frequent nosebleeds, easy bruising, and prolonged bleeding after minor injuries. In recent weeks, he has experienced recurrent upper respiratory tract infections. Three months ago, he was treated with chloramphenicol for bronchitis. No other chronic medications, no hematologic diseases, does not drink or smoke, does not work with chemicals or in a hazardous environment.

Physical Examination

Pale skin and mucous membranes, petechiae and ecchymoses on the forearms and legs, no jaundice, no hepatosplenomegaly, heart rate 96/min, blood pressure 110/70 mmHg. Signs of infection – mildly enlarged cervical lymph nodes, low-grade fever.

Laboratory Tests

HGB 72 g/l, HCT 0.22, MCV 90 fl, MCHC 335 g/l, RET 0.1%, WBC 1.8 $\times 10^9$/l, NEU 0.7 $\times 10^9$/l (normal 2–7 $\times 10^9$/l), PLT 22 $\times 10^9$/l, RTC index below 0.5 (normal above 2), bilirubin and LDH normal.

Bone marrow: hypocellular, fatty degeneration, depletion of all hematopoietic lineages.

1. What are the changes in hematologic parameters?
2. What type of anaemia does the patient have (diagnosis)?
3. What is the etiopathogenesis of this anaemia? Which blood elements are also affected?
4. What additional (non-hematologic) symptoms occur in this type of anaemia?
5. What is the difference between this anaemia and haemolytic anemia?
6. Describe the anaemia according to the morphological classification.

Case Study 5

History: A 64-year-old retired man is being followed long-term for diabetic kidney disease (type 2 diabetes mellitus for more than 20 years). Over the past year, he reports progressive fatigue, pallor, sleepiness, decreased performance, occasional dizziness, and dyspnea. He does not report infections or bleeding. He follows a diabetic diet with restricted protein intake. No hematologic diseases in the past. Medications: metformin, ACE inhibitor, furosemide, insulin. No exposure to cytotoxic drugs.

Physical Examination

Pale, dry skin with mild pruritus, blood pressure 155/90 mmHg, mild ankle oedema, slight urine-like odour on breath (uremic foetor), no signs of bleeding, jaundice, or splenomegaly.

Laboratory Tests

HGB 92 g/l, HCT 0.28, MCV 87 fl, MCHC 330 g/l, RTC 0.4, WBC and PLT normal, S-Fe 9 µmol/l, FER 32 µg/l, TIBC 38 µmol/l, sat.TRF 20%, creatinine 580 µmol/l, urea 28 mmol/l, EPO decreased, bone marrow normal.

1. What are the changes in hematologic parameters?
2. What type of anaemia does the patient have?
3. What is the etiopathogenesis of this anaemia (multiple causes)?
4. Describe the anaemia according to the morphological classification.

Case Study 6

History: An 18-year-old high school student, originally from sub-Saharan Africa, living in Slovakia since childhood. Since early childhood, he has had repeated hospitalizations for bone, chest, and abdominal pain – described as painful crises. He often suffers from fatigue, pallor, and jaundice, especially after infections or dehydration. Last month he was hospitalized after severe pain in the lower limbs and chest following a respiratory infection. His mother is a sickle cell trait carrier (AS), father had sickle cell disease (SS). The patient is taking hydroxyurea and folic acid.

Physical Examination

Pale skin and mucous membranes, scleral subicterus, tachycardia (110/min), tenderness of long bones on palpation, mild splenomegaly (in childhood). In later life is possible autosplenectomy (splenic atrophy due to repeated infarctions).

Laboratory Tests

HGB 85 g/l, HCT 0.26, MCV 88 fl, MCHC 340 g/l, RTC 8%, S-BIL-I 45 µmol/l, elevated LDH, low haptoglobin.

Bone marrow: hypercellular – erythroid hyperplasia.

Blood smear: sickle cells (drepanocytes), target cells, Howell–Jolly bodies.

Haemoglobin electrophoresis: HbS 92%, HbF 6%, HbA2 2%.

1. What are the changes in hematologic parameters?
2. What type of anaemia does the patient have?
3. What is the etiopathogenesis of this anaemia?
4. How does the altered haemoglobin contribute to vasoocclusion?
5. Describe the anaemia according to the morphological classification.

Case Study 7

History: A healthy 35-year-old male pharmaceutical laboratory worker, without chronic diseases. Two weeks ago he was treated for a urinary tract infection – prescribed trimethoprim-sulfamethoxazole (Biseptol). Four days after starting treatment, he developed fatigue, dark urine, jaundice, and lumbar pain. No fever, no bleeding, no weight loss. His father had "yellow eyes and dark urine" after antimalarial medications. No long-term medications, no toxin or alcohol exposure.

Physical Examination

Pale skin and mucous membranes, mild scleral and skin icterus, no splenomegaly or hepatomegaly, heart rate 105/min, temperature 37.5 °C, dark brown urine.

Laboratory Tests

HGB 96 g/l, HCT 0.3, MCV 88 fl, RTC 4.5%, WBC 6.5 $\times 10^9$/l, PLT 220 $\times 10^9$/l, S-BIL-T 64 µmol/l, haptoglobin < 0.1 g/l, LDH markedly increased, Fe normal.

Bone marrow: erythroid hyperplasia.

Coombs test (antibodies against RBCs): positive.

G6PD activity (after crisis): decreased.

1. What are the changes in hematologic parameters?
2. What type of anaemia does the patient have?
3. What is the etiopathogenesis of this anaemia?
4. Describe the anaemia according to the morphological classification.