Diseases of the Hemopoetic system

anemia
polycytemia

trombocytopenia
trombocytosis / trombocytemia

leukopenia
leukocytosis

aplastic anemia / bone marrow failure

myelodysplastic syndrom / MDS
myeloproliferative diseases / MPS
leukemia

Diseases of the Hemopoetic system

investigations

1. peripheral blood, PB
2. bone marrow, BM
3. organs capable of extramedullar hemopoesis
4. organs and tissues affected by the disturbences of hemopoesis

Diseases of the Hemopoetic system

anemie - PB

- hematocrite
- reb blood cell count
- Hb
- size and shape of erythrocytes / anisocytosis, poikilocytosis

anemia - BM

- differential count
- precursors and maturation
  - normoblasts / sideroblasts

biochemical and other findings

- transferin, apoferitin

ANEMIA – DEFINITION

	Hemoglobin (g/l)	**Erytrocytes** (x10^{12}/l)	**Hematocrit** (%)
Men	**< 130–135**	**< 4,2**	**< 38 %**
Women	**< 115–120**	**< 3,8**	**< 35 %**

Anemia – classification

I posthemorrhagic anemias
- acute
- chronic

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II of increased destruction of erythrocytes / decreased survival
- hemolytic anemias
- hypersplenism

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III diseases associated with a production of erythrocytes
- **proliferation and maturation of erythroblasts**
  - impaired synthesis of DNA
  - impaired synthesis of DNA
  - unknown / unclear mechanisms
- **proliferation and differentiation of stem cells**

I. Posthemorragic anemias

acute

external
internal

↓

exsanguination
hypovolemic shock
anemia – restitution, Fe

sources of bleeding

- **arteries** (external x internal) aortic aneurysm rupture
  stomach ulcer
  tbc cavern

- **veins** (external x internal) oesophageal varices

- **organs** (liver, spleen) rupture

I. Posthemoragické anémie

acute
- externa
- internal

↓ exsanguination
hypovolemic shock
anamia – restitution, Fe

chronic
- GIT
- gynecologic
- lungs

→ posthemorragic anemia
+ depletion of Fe^{2+}
sideropenic anemia

organ changes

II. Anemia of increased destruction of erythrocytes / decreased survival

- **decreased survival of erythrocytes**
- **accumulation of catabolic substances**
- **increased erythropoesis** → **in bone marrow ± extramedullary**

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decay of erythrocytes into particular substances

hemoglobinemia - methemoglobinemia → **hemoglobinuria**
methemoglobinuria
hemosiderinuria

hem → ***increased production of bilirubin*** → **icterus**
bile sand
bile stones

iron → **hemosiderosis**

stroma of erythrocytes → **thrombogenic**

II. **Anemia** of increased destruction of erythrocytes / decreased survival

hemolytic anemias

two types of hemolysis

intravascular	Hb nemia – Hb uria – hyperbilirubinemia
extravascular	iron overload – hyperbilirubinemia

Hemolytic anemia

Intracorpuscular anemie

congenital

- defects of membranes
- hemoglobinopathy
- enzymopathy

acquired (PNH)

Extracorpuscular anemia

Congenital spherocytosis

inherited as dominant trait
most frequently north Europe 1 : 5000

mutations of membrane a submembrane proteins of RBC

- ankyrin
- group 3 (band 3)
- spectrin
- protein 4.2

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clinically variable
heterozygotes
combined heterozygotes

stagnation of RBC in the spleen – phagocytosis – splenomegaly
500g -1000g
disruption of membranes – size decrease, depletion K^+
glycogen depletion
decrease of pH

Congenital spherocytosis

clinical and laboratory findings

PK anemia with a typical cytological picture
KD hyperplasia
splenomegaly

hemolytic jaundice

mild forms – almost asymptomatic

severe forms – symptomatic

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during the disease – critical situations / crises:
- bone marrow failure (aplastic anemia)
  (parvoviral infection – damage to normoblasts)
- hemolytic crisis
  (splenic activation, e.g. at IM)

cholelithiasis and its complication

Sickle cell anemia

Thalasemia

adults

HbA	**-** $\alpha 2\beta 2$	96%
HbA2	**-** $\alpha 2\delta 2$	3%
HbF	**-** $\alpha 2\lambda 2$	1%

Thalasemie

beta – defect of β chain
gen na chromosome 16
point mutations
homozygotes x heterozygotes

Thalasemia

alpha – defects of α chain
2 genes in a tandem - chromosome 11
mutations - deletions
homozygotes x heterozygotes

Paroxysmal nocturnal hemoglobinuria

clonal proliferation of a stem cell with a mutated gene:
Phosphatidyl Inositol Glykan Ancor biosynthesis class A (**PIGA)**

protein is necessary for binding – membraneous proteins

covalent binded proteins to cell membranes
GPI (*glykosylphosphatidylinositol*) – fuction of a membrane ancor

Xlinked - Xp22.1 (*PIGA lyonized*) one alele mutation suffices

KD clonal expansion of progenitor cells of all BM hemopoetic cells
persisting normal and pathological hemopoesis

sometimes develops after a bone marrow failure, esp. autoimune induced

Paroxysmal nocturnal hemoglobinuria

- impaired function of
3 proteins preventing complement activation → prevention of hemolysis
- CD55 (DAF)
- binding protein C8
- CD59 (convertase C3 inhibitor)

RBC undergo lysis after an attack of C5b-9 (attack membraneous complex)

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- **chronic hemolysis, PNH in only about 25%**
- **anemia usually mild to moderate**
- **there is iron depletion - hemosiderinuria**

- **risk factors**
  - venous thrombosis ↑↑ – peripheral, hepatic, portal, CNS in up to 40%
  - transformation in AML or MDS 5 to 10 %

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therapy
monocl. anti C5 (Eculizumab) – increased risk of meningococal sepsis
immunosupression, bone marrow transplantation

Hemolytic anemias

- **Intracorpuscular**
  - **congenital**
    - **membrane** defects
    - hemoglobinopathy
    - enzymopathy
  - **acquired (PNH)**

- **Extracorpuscular**
  - **immunohemolytic**
    - warm antibodies
    - cold aglutinins
    - cold hemolysins
  - **traumatization of erythrocytes**
  - **other**

Hemolytic anemias

Extracorpuscular

immunohemolytic

warm antibodies – active at 37°C IgG

primary
secondary
- drug induced – penicilin, cefalosporin
- SLE
- lymphomas e.g. CLL / SLL

cold agglutinins – active below 37°C IgM
- acute at IM, mycoplasma pneumonie, CMV, HIV and other
- chronic
  - primary
  - lymhomas

cold hemolysins – active below 37°C IgG
rare, children – viral infections

traumatization of erythrocytes

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III. Anemia – impaired synthesis of DNA

megaloblastic anemias = lack of folic acid (B9) / vitamin B12

dysbalance: ↓ intake x **↑ demands**

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B12 – pernicious anemia *(Addison-Biermer)*

cause – chronic atrophic gastritis, type A
decrease or absence of the intrinsic factor → depletion of B12

findings –	**GIT**	gastritis, mucosal atrophy
	BM	hyperplasia, megaloblasts, asynchrony, inefective hemopoesis
	PB	anemia, leukopenia, thrombocytopenia
	CNS	funicular myelopathy
	other organs	heart, liver, kidneys, brain

III. Anemia – impaired hemoglobin synthesis

sideropenic anemia (iron defficiency anemia, microcytic)

imbalance: ↓ intake x **↑ demands** x **iron incorporation defects**

III. Anemia – impaired synthesis of hemoglobin / iron defficiency anemie

iron metabolism

intake bound in hem (25%)
free iron (1 - 2%)

transport

storage compartments functional stores

losses 1 – 1,5 mg / day

anemia develops

- foot intake ↓

- demands ↑

- iron incorporation

primary – sideroachrestic

secondary – led poisoning, BM carcinosis

Bone marrow failure / pathology of proliferation and differentiation of stem cells

acquired	**idiopathic**	defects of stem cells immune related ?
	chemically induced **dose related**	alkylating drugs antimetabolites (VCR) chloramfenicol benzene
	idiosyncratic	fenylbutazone chlorpromazine chloramfenikol streptomycine
	physical **virus induced**	HB, CMV, EBV, V-Z
inherited		

Bone marrow failure – carcinosis of bone marrow

Polycytemia - classification

relative — **decrease volume of plasma** (hemoconcentration)

absolute

- **primary**
  - **– polycythemia vera** (MPS)
- **secondary**
  - **– appropriate**
    - high altitude
    - cardiac diseases
    - lung diseases
  - **– inappropriate**
    - neoplasms producing erythropoetin

Thrombocytopenia - classification

decreased production of platelets

generalized BM diseases	**infiltrative** **BM failure**
selective	**drugs** **infections** (rubeolla)
infective megakaryopoesis	**inherited** (W.A. syndrome) **acquired** (megalobl. anemia)

decreased lifespan of platelets

consumptive	DIC, KM syndrome
destruction	**auto ab** (ITP, SLE) **iso aglutinins** **drugs** (heparine) **infections** (EBV, HIV)

platelet sekvestration — **hypersplenism**