Anemia

Anemia is a symptom, not at disease. Always determine the cause

The erythron includes erythropoietic cells in bone marrow and mature erythrocytes in peripheral blood.

Erythrocytes have to maintain internal milieu or else hemolysis will be the result.

Inborn and acquired diseases occur. Acquired due to intake, malabsorption, losses, hypoplasia or atrophy, malignancies, infections, trauma, chemical or physical agents as radiation.

Anemia - definition

Decrease below normal of hemoglobin or erythrocytes in peripheral blood.

B-Hb is most often used
Decreased production or increased consumption to such a degree that production cannot compensate.

WHO:
Hb < 120 g/L adult women
Hb < 110 g/L pregnancy
Hb < 130 g/L adult men
Or decrease from known individual reference value

Symptom

Depends on:
1. Reduction of oxygen carrying capacity
2. Degree of change in blood volume
3. Speed of changes above
4. Manifestations of underlying disease
5. Compensation capacity, cardiovascular and pulmonary. Coronary artery disease usually will lead to earlier symptom debut or make the symptoms more severe.

If gradual change, symptoms will occur at Hb < 80 g/L.

Erythrocyte parameters

- **B-Hb** (Hemoglobin)
- **B-EPK** (Erythrocytes particle concentration)
- **B-EVF** (Erythrocytes volume fraction; hematocrite)

Erythrocyte indices

- **Erc-MCV** (Mean cell volume)
  - (MCV = 10xEVF / EPK) **Volume index**
- **Erc-MCHC** (Mean cell hemoglobin concentration)
  - (MCHC = 100xHb / EVF) **Saturation index**
- **Erc-MCH** (Mean cell hemoglobin)
  - (MCH = Hb / EPK) **Color index**
- **Erc-RDW** (Red cell Distribution Width)
  - (SD / MCV)
Reticulocytes

Very good measure of erythropoesis

Increases quickly, 2-3 days after treatment of megaloblastic anemia, maximum after 5-8 days. After treatment of iron deficiency anemia day 5-10.

Anemia with low/normal levels indicates decreased erythropoesis.

Anemia with increased levels indicates increased consumption.

Reticulocytes

HFR = High fluorescence reticulocytes

HFR are the earliest forms released from the bone marrow.

Characterization of anemia

Size - MCV

• Normocytic
• Mikrocytic (< 7,0 µm)
• Makrocytic (> 8,5 µm)

Color variation, polychromasia

• Normochrome
• Hypochrome

Pregnancy

Plasma volume increases, max around week 24. To avoid dilution increase of erythrocytes. Return to normal 1-3 weeks after partus.

Iron deficiency relatively common, microcytic anemia.

The fetus needs iron, vitamin B₁₂ and folic acid.

A mother with B₁₂-deficiency breast feeding the baby will have a baby with deficiency. Megaloblastic anemia and irreversible neurological damage has been seen in breast fed newborns to vegans and women with pernicious anemia.

Characterization of anemia

Color variation, polychromasia

• Normochrome
• Hypochrome

Children

Different reference intervals compared to adults. Adult levels around 18 years.

True for both Hb and MCV.
**Ethanol**

Macrocytosis common in chronic alcoholics even without anemia. May be due to deficiency of folic acid, liver cirrhosis and direct effects on erythropoiesis of ethanol.

Abnormal vitamin B₆-metabolism occurs. Production of heme is affected by ethanol.

MCV normalizes in 2-4 months during ethanol abstinence.

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**Iron deficiency anemia**

Most common form of anemia.

Long time of negative iron balance. Decreased intake or increased physiologic need.

Especially common in pregnancy and growing children.

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**Iron deficiency anemia**

Decreased intake or malabsorption.

Increased losses due to bleeding, menstruation, blood donation etc.

Gastrointestinal bleeding most common in men, second most common in women after menstruation bleeding.

Increased need during growth. An infant has used all reserves at 2-6 months age.

Increased need during pregnancy and breast feeding.

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**Symptoms**

Main disease, often gradual development of anemia.

Growth disturbance in children.

Tiredness common in iron deficiency/sub clinical iron deficiency. Note! May occur without anemia.

Hb most common 70-80 g/L when the patient complains of anemia symptoms.

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**Epithelial symptoms**

Nails

Tongue - sore, atrophy

Mouth - stomatitis

Hypopharynx – difficulties to swallow

Stomach - achlorhydria, gastritis

**Pica**

Symptom of iron deficiency anemia, may sometimes be the reason for anemia.

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**Laboratory findings**

**Peripheral blood**

- Hypochrome, microcytic anemia with anisocytosis and poikilocytosis.
- Reticulocytes normal to decreased.

**Bone marrow**

- Normal cellularity.
- Normal erythropoiesis, normoblastic.
- Marked reduction of storage iron (depåjärn), marked reduction in number of sideroblasts.
**Laboratory findings**

**Iron status (järnstatus)**
- S-Fe low.
- Transferrin/TIBC high.
- Iron saturation (järnmättnad) low.
- S-Ferritin low, around 3-6 \( \mu \)g/L.
- Ferritin increases in acute phase reaction, may be falsely normal in inflammation.
- Soluble transferrin receptor is one of the future analyses to diagnoses iron deficiency in inflammation.

**Therapy**

Quick subjective improvement.

![Graph showing hemoglobin levels over weeks of therapy](image)

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**Secondary anemia**

Second most common form of anemia. Infections, inflammation, traumatic or neoplastic diseases remaining active during 1-2 months. After this the anemia may be stationary.

Normally the bone marrow increases erythropoiesis 6-8 times but this is not the case in secondary anemia.

**Symptoms**

Depends on the disease.

Correlation between grade of anemia and severity of the disease. More severe anemia in wide spread cancer than in localized cancer.

Weight loss common. Increased protein catabolism, negative nitrogen balance due to proteolysis of muscles.

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**Laboratory findings**

**Peripheral blood**
- Normocytic, normochromic anemia
- Normal reticulocytes.
- MCV usually normal.

**Bone marrow**
- Normal cellularity
- Normoblastic erythropoiesis
- Increased iron storage, marked decrease in sideroblasts

**Laboratory findings**

**Iron status (järnstatus)**
- S-Fe low.
- Transferrin/TIBC low.
- Iron saturation normal.
- S-Ferritin normal or increased

**Miscellaneous**
Inflammatory reaction, increase of acute phase proteins.
Anemia secondary to endocrine disorders

Hypothyroid patients have anemia in 60% of cases. Microcytic combined with iron deficiency. Macrocytic combined with deficiency of B₁₂ and/or folic acid.

Addison: normocytic, normochrome anemia. Hypogonadism may give anemia in males.

Hypophyseal insufficiency may result in a moderate but stable anemia. Severe hypophosphatemia may result in anemia (levels < 0.2 mmol/L (ref 0.7-1.5).

B₁₂- and folate deficiency

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>Proportion in blood</th>
<th>Transport protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transcobalamin</td>
<td>30% of B₁₂ in blood</td>
<td>Transcobalamin II</td>
</tr>
<tr>
<td>Haptocorrins</td>
<td>70% of B₁₂ in blood</td>
<td>R-binders</td>
</tr>
</tbody>
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Etiology to B₁₂-deficiency

- **Gastrointestinal**
  - Chronic gastritis, gastrectomy, or other diseases in the stomach.
  - Pancreatic diseases
  - Resections of small intestine.
  - Celiac, inflammatory intestinal disease

- **Autoimmune**
  - Pernicious anemia, deficiency of intrinsic factor due to auto antibodies towards I intrinsic factor or parietal cells.
  - Autoimmune thyroid diseases
  - Diabetes, vitiligo

- **Drugs**
  - All drugs reducing acid content in stomach

- **Low intake**
  - Uncommon – increasing frequency?
  - Strict vegans. Breast fed children to vegans.

- **Infection**
  - Fish tape worm (bandmask), HIV.

- **Misc**
  - Laughing gas (NO₂, lustgas)

Methyl malonic acid (MMA) and B₁₂

- Methyl malonic acid
**Factors influencing P-Homocysteine**

- Smoking
- Coffee (all kinds - även bryggkaffe)
- Impaired renal function
- Impaired liver function
- High ethanol consumption
- Deficiency of B12 and folate, to some degree B6
- Antiepileptic drugs – almost always folate deficiency
- Folate antagonists – methotrexate, trimetoprim

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**Homocysteine – blood sampling**

- Body position: protein bound
- Diurnal variation: fasting sample not needed, recommended in some cases, especially studies. Slightly lower in the morning.

**Centrifugation immediately, stable in plasma at room temperature, at +4°C and in freeze.**

Erythrocytes produce homocysteine.

- EDTA/serum: Centrifugation immediately
- Li-Heparin: Less sensitive
- Acid citrate: Stable after sampling

**Factors influencing P-Homocysteine**

- Hereditary factors (MTHFR, CBS)
- Increases with age
- Higher in males
- Increases after menopause
Homocysteine – reference interval

0-12 years (and in pregnancy)
< 10 µmol/L (5-10 µmol/L)

>12 years
< 15 µmol/L (5-15 µmol/L)

Homocysteine is a strong, independent risk factor for Alzheimer disease. No prevention studies available.

Neurological effects
Folate deficiency is associated with dementia and depression. Effects are seen on mood and social and cognitive function. Important for the nervous system in all ages. Might influence aging of the brain in elderly.
Reynolds EH. J Neurol Neurosurg Psychiatry 2002; 72: 567-571
Reynolds EH. BMJ 2002; 324: 1512-1515

RDI for folate appr 400 µg/day in the US
Different RDI depending on MTHFR genotype?

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Reynolds EH. J Neurol Neurosurg Psychiatry 2002; 72: 567-571
Reynolds EH. BMJ 2002; 324: 1512-1515

Pregnancy and B12/folate
Strict vegans without vitamin substitution
Risk diet for development of B12 deficiency in mother and fetus!
Increased homocysteine levels associated with:
- vascular disease
- NTD (Neural tube defects) in children
- recurrent early spontaneous abortions
- congenital heart anomalies
- schisis
- vascular diseases, eg in placenta
- preeclampsia

Mutations in MTHFR

677 TT or combined heterozygotes 677 CT + 1298 AC

Increased risk for:
- NTD in children
- recurrent spontaneous early abortions
- vascular conditions

Folate supplementation and NTD

Supplementation must begin 4 weeks before conception.
To late when pregnancy test is positive

Approx 900 women must be given folate to prevent one case of NTD
Might add 5-6 extra twin births.
Lumley J et al. BJOG 2001 Sep;108(9):937-42.

Twin births and MTHFR

Mothers with 677C→T mutation had a 2.28-fold lower risk for twin births compared to those without mutation.
(95% confidence interval = 1.18-4.66; P = 0.008)

Fertility

S-Folate ≤ 4.9 nmol/L had an increased risk for spontaneous abortions. OR 1.47 (1.01 – 2.14)
George et al. JAMA 2002 vol 288, 1867-1873

B12-deficiency increases the risk for early and very early recurrent abortions (miscarriages).

Reduced fertility in female dental assistants exposed to high levels of laughing gas (lustgas).
NEJM 1992 vol 327, 993-997
Recent meta-analyses

30 studies, 5073 events of ischemic heart disease (IHD) and 1113 cases of stroke. Elevated homocysteine moderate independent predictor. 3 umol/L lower level associated with reduced risk - odds ratio 0.89 (0.83-0.96) for IHD and 0.81 (0.69-0.95) for stroke. Studies January 1966-January 1999.


40 studies, 11162 cases and 12758 controls. Individuals with MTHFR 677C-T polymorphism had higher risk for coronary heart disease, especially in case with low folate levels. Odds ratio 1.16 (1.05-1.28). Articles published before June 2001.

Klerk M et al. JAMA 2002; 288: 2023-2031

Risk marker = an attribute or an exposure coupled to increased risk for disease without causal connection.

Risk determinant = an attribute or an exposure coupled to increased risk for disease, a causal connection might exist but is not proven.

Risk factor = a risk determinant which probably is causally coupled to increased risk for disease and if modified may modify the risk for disease.

Dahlqvist, G. Läkartidningen, vol 97, nr 4, 2000; 313-315

Percutaneous coronary intervention

Reduced coronary restenosis after reduction of homocysteine levels with 1 mg folate, 400 µg B12 and 10 mg B6 during 6 months.

Schnyder G et al. NEJM; 345: 1593-1600

Reduced frequency of death, non-fatal myocardial infarction, need for revascularization. Evaluated after 6 months and 1 year.

Schnyder G et al. JAMA 2002; 288: 973-979

Conclusions

• B12 deficiency may occur at low, "normal" or high levels of B12 in blood.

• Folate deficiency may occur at low levels and in the lower reference range.

• Deficiency of B12 and folate are revealed by homocysteine.

• Methyl malonic acid only finds B12 deficiency.

• Homocysteine is an independent risk marker for atherosclerotic and thrombotic disease.

Prevention studies

Folate: 0.2 - 5 mg
B12: 0 - 1 mg
B6: 0 - 50 mg

Placebo differs from placebo to multivitamins.

www.rondellen.net (English version)
Megaloblastic anemia in form of pernicious anemia

Relatively common in Scandinavia, 9-17 new cases / 100 000 every year, 0.13 – 0.20 % prevalence. Females more common, late in life.

Often atrophic gastritis – deficiency of intrinsic factor. Hereditary! Auto antibodies common. May also be mediated by T-cells. Increased frequency of other autoimmune diseases.

Megaloblastic anemia is a macrocytic anemia with reduced DNA synthesis that gives an unbalanced cellular growth where RNA-synthesis is intact but cellular division is limited. Most often caused by deficiency of the B-vitamins B12 and folate.

Symptoms

Neurological symptoms are most common the earliest. Hematological symptoms are late or terminal symptoms of B₁₂-deficiency.

Slow to present, coming gradually. Anemia often more accentuated than the symptoms.

Fatigue, parestesias, sore tongue.

Laboratory findings

**Peripheral blood**

HB may be as low as 50 g/L in some cases. Symptoms of anemia at 70-80 g/L.

MCV high, erythrocytes macrocytic, normochromic.

Increased fragmentation of erythrocytes, anisocytosis, poikilocytosis. Inclusions in erythrocytes may occur, eg basophil punctuations, Howell-Jolly bodies, rarely Cabot's rings. Nucleated red cells (kämförande röda). Leucocytes normal/decreased. Hyper-segmented neutrophil granulocytes increased. Thrombocytopenia may occur. Reticulocytes normal.

**Bone marrow**

Cellularity increased, hyperplastic marrow, erythropoiesis dominates.

Megaloblasts are seen, big cells, basophilic cytoplasm, smooth decaying nucleus (rotten ice). Mitoses increased, caryorrhexis. Granulopoesis shows maturation disturbances, especially non nucleated giant forms may be seen. Megakaryocytes may be reduced or present with abnormal nuclei. Storage iron increased. Sideroblasts increased.

**Laboratory findings**

 Iron increased, ferritin increased. Haptoglobin low. Bilirubin may be increased. Lactate dehydrogenase increased.

These findings also seen in hemolytic anemias. Megaloblastic anemia has hemolytic features.

Laboratory findings

S-Folate low, sometimes in lower reference interval. Erc- or B-Folate was earlier considered a better parameter, this is now in doubt. S-Folate will find more individuals with deficiency. S-Vitamin B₁₂ low, normal and high. Low levels most common. P-Homocysteine increased. S-Methyl malonic acid (MMA) increased.
**Laboratory findings**

- Hematological changes often late.
- Pepsinogen and gastrin in serum – indicators of decreased gastric function.
- Antibodies towards intrinsic factor and endomysium - autoimmune component.
- Small intestinal biopsy - B12-malabsorption.
- Tests above won’t diagnose deficiency, may give information of causes or predisposition.
  (Schilling test not needed anymore!!)

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**Hemolytic anemias**

- Increased destruction of erythrocytes.
- Compensational 6-8 increase in production not sufficient.
- Life span of erythrocytes reduced from 120 to 15-20 days.

- **Bone marrow hemolysis**
- **Peripheral hemolysis**

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**Hemolytic anemias**

**Inborn forms – defect erythrocytes**

**Membrane defects**
- Hereditary spherocytosis
- Hereditary elliptocytosis

**Enzymatic defects**
- Glukos-6-fosfat-dehydrogenase deficiency
- > 20 other enzymatic defects

**Hemoglobinopathy**
- Sickelcellanemi

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**Hemolytic anemias**

**Acquired forms, external mediated erythrocyte damage**

**Immune mediated**
- Warm/cold autoimmune hemolytic anemia
- RH-immunization or other pregnancy immunization

**Non-immune mediated**
- Traumatic / mechanic
- Microangiopatic
- Hypersplenism
- DIC
- Infectious agents
- Chemicals, toxins

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**Symptoms**

- Depends on duration / severity.
- Acute hemolysis may resemble acute fever disease. Back pain, headache, stomach pain, paleness, yellow complexion (gulsot), tachycardia, severe anemia.
- More often gradual symptoms are seen. Often slow progression of anemia.

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**Laboratory findings**

**Qualitatively:**
- Erythrocyte morphology in peripheral blood.
- P-Haptoglobin
- DAT (direct antiglobin test = Coombs direct test)

**Quantitatively:**
- S-Lactate dehydrogenase
- S-Bilirubin, unconjugated (direct reacting)
- B-Reticulocytes
- In some case B-COHb – not in smokers!
Laboratory findings

Bone marrow

- Cellularity increased. Normoblastic erythropoiesis dominates, erythroid hyperplasia.

- Storage iron increased, marked increase in sideroblasts. Siderocytes (erythrocytes with iron) increased in number.

Laboratory findings

- S-Fe increased, transferrin / TIBC increased, iron saturation (järnmättnad) increased.

- S-Ferritin increased.

- Bilirubin increased. Haptoglobin decreased.

- HbA1c decreased due to shortened survival of erythrocytes.

- Lactate dehydrogenase increased because of increased destruction of erythrocytes.

- Reticulocytes increased.

Hereditary spherocytosis

Frequency 1 % in Norway and Germany. Diagnosis with osmotic resistance test. (Earlier frequencies around 0.02 % has been reported based on microscopy.)

Sometimes anemia, moderate enlarged spleen, sometimes icterus.

Hereditary spherocytosis

Defect spectrin / ancyrin in erythrocyte membranes. Dominant hereditary, some forms are recessive.

Laboratory:

- Reticulocytes increased

- Bilirubin increased

- Haptoglobin reduced.

- Sometimes increased MCV

- Decreased osmotic resistance.

- Sometimes anemia.

- Increased storage iron.

- Splenectomy if severe symptoms.

Osmotic resistance test

Test erythrocyte osmotic fragility. In hereditary spherocytosis decreased osmotic resistance.

Test is performed both before and after 24 hours incubation at 37°C to deplete the erythrocytes of glucose. Increase sensitivity after 24 hours.

Flow cytometric testing an alternative.
Hereditary elliptocytosis

Often slight hemolysis. Anemia in severe cases. Splenomegaly och gall stone disease may occur.

Normal osmotic resistance. Defect cytoskeletal protein.

0.1-1.0 % of the population.

Non-spherocytic hereditary anemias

May be due to enzymatic defects. Glucose-6-phosphate-dehydrogenases (G6PD) relatively common. Also called favism. Individuals sensitive to some drugs and to the fava fava bean (bondböna).

Other enzymatic defects are uncommon.

G6PD-deficiency

Glucose-6-phosphate-dehydrogenase-deficiency

Enzymatic defect in 100 million males in the world. Sardinia 15%. 10% in some Greek regions.

Reduced synthesis of ATP, leading to impaired function in membrane stabilizing ATP-dependent protein kinases. May result in membrane rigidity which would increase risk of hemolysis.

Autoimmune immune hemolytic anemia

Increased destruction because of auto antibodies to own erythrocyte antigens.

Often part of autoimmune syndrome or lymphoproliferative disease. Sometimes because of drugs or infection.

"Warm"
Antibodies binding to erythrocytes at 37ºC.

"Cold"
Binds at lower temperatures.

DAT ( = Coombs test )

Normal

\[ \begin{array}{c}
\text{Normal} \\
\text{+ Anti-immunoglobulin antibodies}
\end{array} \]

With auto antibodies

Autoimmune immune hemolytic anemia

"Warm"
Autoimmune or lymphoproliferative
Idiopathic

"Cold"
Lymphoproliferative diseases
Infections – mycoplasma, mononucleosis
Idiopathic
Rh-immunization
One of the most common causes of immune hemolytic anemia in newborn.
Antibodies towards the Rh-complex – CDE genes - from the mother's circulation pass the placenta to the fetus.
Prophylaxis must be given at partus. Risk of transfer of fetal blood and immunization of the mother. Gives problems in the next pregnancy.
Other blood group antigens may also give hemolysis.
All pregnant women are followed during pregnancy to find immunization.
Blood exchange sometimes needed in newborns.

Paroxysmal nocturn hemoglobinuria
PNH
Acquired hemolytic condition with intra-erythrocytic cause.
Hematopoetic stem cell clone with defect protein anchor disabling the binding of surface proteins that are supposed to protect from complement activation.
Complement activation increases risk for lysis of cells.

Paroxysmal nocturn hemoglobinuria
PNH
The diagnosis was earlier made by the unspecific Hams test.
Today flow cytometric analysis of peripheral blood is performed.
Läkartidningen 1997, volym 94, sid 4323-4326

Paroxysmal nocturn hemoglobinuria
PNH
Symptoms of hemolysis
Complications:
• Pancytopenia, aplastic anemia
• Thromboembolic manifestations
• Myelodysplastic syndrome
• Acute leukemia

Hemoglobinopathy and thalassemias
Hemoglobin consists of four globin sub-units. Two are α-chains.
In adults > 95 % should be HbA (α2β2). 2-3 % may be HbA2 (α2δ2).
More than 450 different hemoglobin variants are known. 50 % have no symptoms.
Other may result in functional disturbances as instable hemoglobin, change in oxygen binding affinity, intracellular aggregation of formation of methemoglobin.
Prenatal diagnostic tests in severe cases.
**Hemoglobinopathy and thalassemias**

**Thalassemia minor most common.**
- Microcytic, hypochrome anemia.
- S-Fe often normal or high. S-Ferritin normal or high.
- Storage iron normal – high. No response to iron treatment.

**Thalassemia major more severe.**
- Often combination of hemolysis and ineffective production.
- Early debut, 3-6 months after birth.

Diagnose:
- Hb-Electrophoresis: isoelectric focusing of hemoglobin.
- Quantification of HbF and HbA2.

**Sickle Cell Anemia**

Carriers of the disease are usually without symptoms.

In some cases crisis may occur – anoxia or severe infections. HbS then aggregates and the blood cell sickles. Is thought to protect towards malaria.

Homozygotes have severe disease, hemolysis, infarction of organs. Debut in the first year after birth.

**Sports anemia**

Runners. 50 % of running athletes and amateurs with running regularly had iron deficiency in a study.

To low intake of iron common cause.

Slight hemolysis in the soles of the foot.

Haptoglobin may decrease.

March-hemoglobinuria was defined for the first time in 1881 when predisposed individuals were affected after longer physical activity.

**Hypoplasia / aplasia**

Pancytopenia = reduction of all cells in blood – erythrocytes, leukocytes and platelets.

Causes:
- autoimmune diseases
- processes infiltrating and taking over normal bone marrow
- aplastic / hypoplastic anemia

**Aplastic anemia**

**Definition**

Reduction of all three poesis (erythropoesis, myleopoesis and thrombopoesis) with an aplasia/hypoplasia in bone marrow without other processes causing the condition.

For diagnosis other causes must be excluded.

**Drug effects**

Many drugs may result in bone marrow inhibition.

One or all poeses may be affected.

Reversible of irreversible.
**Agranulocytosis**

Granulocytopenia, \(< 1,5 \times 10^9/L\). Severe infections may occur \(< 0,5 \times 10^9/L\).
- Decreased production (marrow damaged by infections, drugs, displacement by tumors, fibrous tissue (bindväv) storage disease, vitamin deficiency).
- Increased losses / redistribution (autoimmune diseases, infections, hyperthyreosis).
- Impaired function (hereditary, ethanol, diabetes)
- Treatment of the disease normalizes the granulocytopenia.

**Thrombocytopenia**

Decreased number of platelets. Primary hemostasis affected.
- Reasons:
  - Decreased production (aplasia, infiltration, toxic inhibition).
  - Increased losses (antibody mediated - ITP, increased consumption in acute and chronic DIC.
- Hereditary or acquired forms (uremia, drugs).

**Idiopathic thrombocytopen purpura (ITP)**

Most common form of antibody mediated thrombocytopenia.
- Increased peripheral consumption.
- Increased production in bone marrow.
- Treated with corticosteroids. Usually good prognosis. Seldom spontaneous bleeding.
- Platelet concentrate is given only in cases of bleeding.

**Pseudo thrombocytopenia**

Platelet aggregates in EDTA-test tubes (blood status tubes) gives low levels.
- Artifact in the tube, seen occasionally in healthy individuals.
- Control in citrated test tube gives the right value (note the result is diluted with 10 % citrate).

**Referenser:**

- *Läkemedelsboken aktuell utgåva*
- *Rondellen*, tidskrift om B12, B6 och folsyra: www.rondellen.net