

Coagulation disorders

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Coagulation (clotting)

- is the process by which blood changes from a liquid to a gel
- It results in hemostasis, the cessation of blood loss from a damaged vessel
- vessel contraction
- activation, adhesion, and aggregation of platelets
- hemocoagulation – fibrin formation

Coagulation disorders

- hypo – coagulation: platelets, coagulopathy
- hyper – coagulation: platelets, trombophilias

Bleeding disorders: coagulopathy

- **coagulation factors deficiency**
 - inherited: hemophilias
 - acquired: vit K deficiency, malabsorption, liver cirrhosis, VKA therapy
- **immunocoagulopathy**
 - antibodies formation (LE antibodies, after treatment with coag.factors)
- **consumption of factors**
- **hyperfibrinolysis**
 - DIC, fibrinolytics treatment, alfa2plasmin inhibitor deficiency, tumours surgery (prostate, uterus, lungs, pancreas)

Hemophilia A

- X-linked, recessive disorder
- caused by deficiency of functional plasma clotting factor VIII (FVIII)
- inherited or new spontaneous mutation
- Clinical presentation dependent on FVIII level:
 - Easy bruising, risk of hemorrhage during surgery (mild, >5% of proper level FVIII)
 - Inadequate clotting after traumatic injury (moderate 1-5%)
 - Spontaneous hemorrhage (epistaxis, mouth bleeding, gastrointestinal bleeding, hematuria, bleeding into muscles, joints...) (severe < 1% of proper level FVIII)

Hemophilia A

Expected laboratory values are as follows:

- Hemoglobin/hematocrit: Normal or low
- Platelet count: Normal
- Bleeding time and prothrombin time: Normal
- Activated partial thromboplastin time (aPTT):
Significantly prolonged in severe hemophilia, but may be normal in mild or even moderate hemophilia
- 1/10.000 boys

Treatment: FVIII treatment may be given prophylactically 3 times/week (maintain level of f.VIII > 1% or on demand. Mostly start therapy after first bleeding

CAVE: risk of f.VIII inhibitors occurrence!

Hemophilia A

For treatment of **acute bleeds**, target levels by hemorrhage severity are as follows:

- Mild hemorrhages (early hemarthrosis, epistaxis, gingival bleeding): Maintain FVIII level of **30%** of proper values
- Major hemorrhages (hemarthros or muscle bleeds with pain and swelling, prophylaxis after head trauma with negative findings on examination): Maintain FVIII level of at least **50%** of proper values
- Life-threatening bleeding episodes (major trauma or surgery, advanced or recurrent hemarthros): Maintain FVIII level of **80-100%** of proper values

Hemophilia B

- **Christmas disease**, 20% of hemophilia cases
- an inherited, X-linked, recessive disorder
- deficiency of functional plasma coagulation **factor IX**
- Spontaneous mutation and acquired immunologic processes can result in this disorder as well
- The hallmark of hemophilia is hemorrhage into the joints
- leads to long-term inflammation and deterioration of the joint (typically the ankles in children, and the ankles, knees, and elbows in adolescents and adults), resulting in permanent deformities, loss of mobility, and extremities of unequal lengths
- **Treatment**: Recombinant factor IX is the preferred source for replacement therapy.

Hemophilia C

- deficiency of factor XI
- Even in severe deficiency of factor XI, the bleeding tendency is mild
- rare

Acquired hemophilia

- spontaneous autoimmune disorder
- patients with previously normal hemostasis develop autoantibodies against clotting factors
- 1 – 2 pat/1 mil inhab/year (10-15 pat in CR/year)
- FVIII, FIX, FII, FVII, FX, FXI, FXIII
- Pregnancy and post-delivery, IBD, psoriasis, hepatitis, RA, SLE, malignancies
- hemorrhage into the skin, muscles, or soft tissues and mucous membranes
- Muscle bleeding episodes can be severe and can lead to compartment syndrome and tissue death
- prolonged postpartum bleeding, excessive bleeding following surgery or trauma, and, occasionally, cerebral hemorrhage

Acquired hemophilia

- The level of coagulation factors does not correspond with bleedings
- Treatment:
 - 1/ stop the bleeding – f VII (NovoSeven), aPCC (FEIBA) – FII,IX,X,VII – bypassing the FVIII
 - 2/ prevention of bleeding – postpone surgical procedures, avoid iv and im injections
 - 3/ elimination of inhibitor – immunosuppression (corticosteroids, cyclophosphamide), rituximab (after delivery), immunoabsorption, plasmapheresis in life-threatening bleeding

Hemophilias of all types:

- **Dg**: family history, type of bleeding, lab studies (aPTT, levels of FVIII....)
- **Prevention** of hemorrhage very important!
- Do not apply i.m. injection
- Do not use aspirin in the treatment
- Prevention of bleeding in case of surgery
- **Therapy**: Substitution of coagulant factors

Platelet disorders

Immune thrombocytopenic purpura

- one of the most common autoimmune disorders
- caused by autoantibodies to platelets
- antigenic target in most patients appears to be the platelet GP IIb/IIIa complex
- Platelets with antibodies on their surface are trapped in the spleen and removed by splenic macrophages
- mechanism of origin of these antibodies is not known (cross reaction against viral antigens?)
- antibodies can also react with the developing megakaryocytes in the bone marrow, leading to decreased production of platelets (ineffective thrombopoiesis)

Acute ITP

- affects males and females equally
- has a peak incidence in children aged 3-5 years
- Most patients have a history of an antecedent acute viral syndrome
- Bleeding is usually mild, until the platelet count drops below $20 \times 10^9/l$
- petechiae and ecchymoses are observed following mild trauma **$20 - 50 \times 10^9/l$**
- platelet counts **less than $10 \times 10^9/l$** , generalized petechiae, ecchymoses, and mucosal bleeding occur
- platelet counts **below $2 \times 10^9/l$** , widespread ecchymoses, hemorrhagic bullae, and retinal hemorrhage occur

Acute ITP

- Life-threatening bleeding requires conventional critical care interventions
- high-dose parenteral glucocorticoids
- IV immunoglobulin (IVIg)
- Platelet transfusion (platelet survival is increased if the platelets are transfused immediately after IVIg infusion)
- 1 U of platelets increases count of a 70-kg adult by 5-10,000
- Adults with platelet count $>50 \times 10^9/l$ do not require treatment

Chronic ITP

- is typically observed in adults aged 20-40 years
- has an insidious onset, and a history of an antecedent infection need not be present
- more common in females than in males
- the bleeding manifestations depend on the platelet count (same as acute ITP)
- diagnosis of ITP is established by the exclusion of other causes of thrombocytopenia

Posttransfusion purpura

- Platelet GP IIb/IIIa is a major antigen in platelets
- purpura typically occurs 10 days following a transfusion
- can be induced by a small amount of platelets contaminating a red blood cell transfusion or, occasionally, following fresh frozen plasma (FFP) transfusion
- responds to intravenous immunoglobulin (IVIg)

Drug-induced thrombocytopenia

- Drugs can induce thrombocytopenia by a number of mechanisms
- inhibiting platelet production in the bone marrow (thiazide diuretics, interferon, alcohol)
- immunologic destruction of platelets (amiodaron, captopril, sulfonamids, cimetidine, tamoxifen, vankomycin...)
- diagnosis of drug-induced thrombocytopenia is often empirical
- Recurrent thrombocytopenia following reexposure to the drug confirms the drug as the cause of thrombocytopenia

DIC

- systemic activation of blood coagulation
- 1/generation and deposition of fibrin and microvascular thrombi in various organs contributing to multiple organ dysfunction syndrome (MODS)
- 2/consumption and exhaustion of coagulation proteins and platelets may induce severe bleeding
- 3/accelerated fibrinolysis may cause severe bleeding
- **patient with disseminated intravascular coagulation (DIC) can present with a simultaneously occurring thrombotic and bleeding problem, which obviously complicates the proper treatment**

Causes of DIC

secondary to an underlying disorder

- Sepsis and severe infection (septic shock)
- Trauma (neurotrauma)
- Organ destruction (eg, pancreatitis)
- Malignancy
- Severe transfusion reactions
- Obstetric complications – amniotic fluid embolism, abruptio placentae, HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelets), eclampsia, retained dead fetus
- Vascular abnormalities – Kasabach-Merritt syndrome
- Severe hepatic failure
- Severe toxic reactions, snake bite, transplant rejection
- Heat stroke and hyperthermia

DIC – physical examination:

- Signs of spontaneous and life-threatening hemorrhage
- Signs of diffuse or localized thrombosis
- Bleeding into serous cavities
- Hypotension, tachycardia, circulatory collapse
- Signs of azotemia and renal failure – acidosis, hematuria, oliguria
- Petechiae, purpura
- Jaundice (liver dysfunction or hemolysis)

DIC – lab studies:

- Thrombocytopenia (in 98% patients)
- aPTT and prothrombin time prolonged
- hypofibrinogenemia
- D dimers and FDP elevated
- AT III level decreased

DIC – management:

- Monitor vital signs
- Assess and document the extent of hemorrhage and thrombosis
- Correct hypovolemia
- Administer basic hemostatic procedures when indicated
- treatment of underlying disorder
- heparin, AT III
- fresh frozen plasma

Hypercoagulability

- patients more likely develop clots, venous and arterial thrombosis than healthy individuals
- often a history of recurrent thromboembolism, thrombosis at a young age, and a family history of thrombosis
- **thrombophilias** are inherited hypercoagulable disorders
- **acquired risk factors** for hypercoagulability and thrombosis

Acquired risk factors for hypercoagulability and thrombosis = Virchow's triad

- blood stasis – immobilisation, Paris plasters, leg orthosis, hemiplegias
- injury of the vessel wall (injury of the endothelial cell – surgery, sepsis)
- hypercoagulability – hormonal use, diabetes, pregnancy, obesity, cancer, lupus anticoagulant, advanced age

Thrombophilias = inherited

<u>Condition</u>	<u>Prevalence in General Population, %</u>	<u>Relative Risk of VTE, %</u>
Factor V Leiden	3-7	4.3
Prothrombin 20210A	1-3	1.9
Protein C deficiency	0.02-0.05	11.3
Protein S deficiency	0.01-1	32.4
Antithrombin III deficiency	0.02-0.04	17.5

Thrombophilic disorders

- are usually associated with venous thrombosis
- protein S, protein C, ATIII deficiencies, and lupus anticoagulants have been associated with arterial thrombosis
- patients with protein C and S deficiencies can develop warfarin-induced skin necrosis

Lupus anticoagulants

- acquired, but sometimes classified as thrombophilia
- occur in about 20% of patients with systemic lupus erythematosus
- may occur in patients taking phenothiazines, phenytoin, hydralazine, quinine, amoxicillin, and oral contraceptives
- „anticoagulant“ – false prolongation of the lab test of APTT
- But clinically significant hypercoagulation

Workup in patients with suspect thrombophilia

Especially needed in cases of:

- history of recurrent thromboembolic episodes
- thromboembolism at a young age (< 40 y)
- family history for thromboembolism
- thrombosis in an unusual site

Idiopathic venous thrombosis is defined as venous thromboembolism without any obvious risk factor. About 50% of patients with idiopathic venous thrombosis have an underlying thrombophilia

What to screen

- D dimers
- Lupus anticoagulant
- Levels of AT III, protein C, protein S
- APC resistance
- Genetic studies of F II, F V Leiden mutations

- Screen for malignancies!!!