Acquired disorders of haemostasis

Acquired platelets disorders

- thrombocytopathy
- thrombocytosis
- thrombocytopenia
  - Immune cause:
    - Auto-immune (ITP)
    - Alo-immune (fetal, post-transfusion)
    - HIT
    - Antiphospholipide syndrome
  - Non-immune cause:
    - Decreased production – toxic, infection, medicaments, TU, shortage of folate, B12
    - Increased consumption - DIC, TTP, HUS, MAHA, HELLP, Kassabach-Merritt syndrome
    - Distribution disorders - hypersplenism, hyperthermia

Acquired thrombocytopathy

- Aim of treatment:
  - ASA – COX inhibition
  - clopidogrel, prasugrel, ticagrelor – inhibition of ADP inducet aggregation
  - direct GP IIb/IIIa blocators
- as treatment side-effect: NSAID
- uremia – guanidinsukcinyl acid
  - decreased adhesion, aggregation, metabolism
- paraprotein – decreased adhesion, aggregation
- myeloprolipherative disorders:
  - production of hypofunctional platelets, acq. vWSy

Acq. thrombocytosis

- reactive:
  - infection, malignancy, inflammation, stress
  - sideropenia
  - after splenectomy
  - active bleeding
- essential thrombocytemia:
- other myeloprolipherative disease
  - CML, myelofibrosis, polycytemia vera

Acq. coagulopaties

- liver disease
- malignancy
- paraprotein
- uremia
- K vitamin deficiency (+ warfarin)
- UFH + LMWH treatment
- OC (oestrogene, gestagene)
- sepsis
- DIC
- acq. specific inhibitors (FVIII)
- APS (LA, ACLA)

Liver disease

- Decreased production of plazmatic factors
- Productions of abnormal proteins
- Hypersplenism – pancytopenia
- ↑ PT, ↓ fibrinogen , ↓ AT III, ↓ **platelets** (leu, Hb), ↑ MCV
- Hypofunction of monocyto-macrofag systeme in liver
- Activation of fibrinolysis
- Chronic DIC
- Rarely acq. inhibitors

Malignancy

- demage of vessel wall (infiltration by tumor, hyperviskosity, leucostasis)
- trombocytopenia (infiltration of bone marrow, treatment, hypersplenism, DIC)
- chronic DIC (paracoagulation activity of tumor cells)
  - Expression of TF:
    - by tumor cells
    - by activated leucocytes
  - Enzymes with coagulation activity
  - MAHA
- defect of plasmatic coagulation factors (liver infiltration)
- activation of fibrinolysis (proteolytic activity of tumor cells)

Monoclonal paraprotein

- binding to platelets and coagul. factors
- interference with binding platelets to endothelium
- amyloid – sec. deficiency of FX
- as specific antibodies against coagulation factors
  - inhibitor of vWF, FVIII
- inhibition of fibrin formation
- hyperviscosity

Uremia

- Hypofunction of primary haemostasis
  - platelets (guanidinsukcinyl acid)
  - metabolism of endothelium (↑ PGI_2,NO)
  - interference with binding platelets to (sub)endothelium
  - vessel abnormities – angiodysplasia
- imbalance of plasmatic coagul. factors
  - ↑ FVIII, fbg, AT
  - ↓ PC, PS
  - ↓ fibrinolytic activity

Shortage of K vitamin

- hypofunction of coagul. factors:
  - II, VII, IX, X
  - PC, PS
- prolongation of PT, less aPTT
- in newborns
- warfarin
- antibiotics, parenteral alimentation, obstructive icterus
- treatment:
  - K vitamin
  - PCC, FFP

Pregnancy:

- ↓ PS
- ↑ Fbg, FVII, FVIII, vWF

OC:

- ↑Fbg, FVII, FVIII, vWF
- ↓ PS, AT III

Stress:

- ↑Fbg, FVII, FVIII, vWF
- ↑tPA
- ↓α2AP, Plg

Inflamation

- ↑ **Fbg, FVII, FVIII, vWF**
- ↑ α1AT, PAI-1, tPA, α2MG, Plg

Sepsis

- **Demage of endothelium**
- **Activation of monocytes, granulocytes, expression of TF**
- **Activation of platelets**
- **DIC**
  - **↓ fibrinogen, procoagulation factors and inhibitors of coagulation**
  - **↓ platelets**

Acq. thrombophilia

- Defect of inhibitors (AT, PC, PS, APCR)
- Increase of FVIII, fibrinogenu
- increase PAI - 1
- hyperhomocysteinemia

Disseminated intravascular coagulation DIC

Definition by ISTH:

- is an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes
- it can originate from and cause demage to the microvasculature, which, if sufficiently severe, can produce organ dysfunction

Disseminated intravascular coagulation
DIC

- **Systematic activation of coagulation**, which generates intravascularly **fibrin**
- **Microvascularly thrombotization** of various organs
- **Multiorgan failure**

DIC - etiology

- release of TF:
  - tissue damage (trauma, burns, obstetric)
  - by tumor cells
  - by macrofages and monocytec (sepsis)
- endothelial damage:
  - endotoxin (sepsis)
  - hemangiomas
  - vasculitis
- contact with foreign surface

DIC - clinical manifestations

Acute (de-compensated)
„overt“

- rapid progress
- symptomatic
  - **microthrombotization**
- serious condition
- difficult therapy
- high mortality

Chronic (compensated)
„non-overt“

- slow progress
- asymptomatic
  - **hypocoagulation**
- chronic disease
- therapy mostly not needed

DIC – organs microtrombotization

- skin - haematomas, wound bleeding
  - necrosis
- lung - hypoxia, shortness of breath
- Kidney - proteinuria, iligo-, anuria, failure
- liver - failure
- pituitary gland - fever
- supraren. gland - hypotension, ionic dysbalance

DIC - laboratory tests

Screening tests

- fibrinogen
- platelets
- prothrombin time (PT)
- activ. parc. thromboplastin time (aPTT)

DIC - laboratory tests

Specific tests:

Procoagulant activity

- ***EGT,*** *F1+2, FPA, FM, TAT, DD*

Fibrinolytic activity

- ***DD,*** *FDP, plasmin, PAP*

Inhibitors consumption

- ***ATIII***, **PC**, *α-2-antiplasmin, PS, TAT, PAP*

Organs failure

- ***creatinin, JT, pH, pO2, LD***

ISTH: overt DIC diagnostic scoring scheme

- Condition is presence of causal disease

• platelets(10^9/l)	> 100 = 0	50-100 = 1	< 50 = 2
• fibrin mark. (DD,FDP)	neg. = 0	mild↑ = 2	severe↑ = 3
• ↑ PT by	< 3 s = 0	3-6 s = 1	> 6 s = 2
• fibrinogen (g/l)	> 1 = 0	< 1 = 1	

- ≥ 5 point = overt DIC

ISTH: non-overt DIC diagnostic scoring scheme

1. Risk assessment: does the patient have an underlying disorder known to be associated with DIC?
   yes = 2, no = 0

2. Major criteria

Platelet Count	>100x10^9 l^{-1} = 0 ☐	<100x10^9 l^{-1} = 1 ☐
PT Prolongation	<3 s = 0 ☐	>3 s = 1 ☐
Fibrin related-markers	Normal = 0 ☐	Raised = 1 ☐

Rising = –1 ☐	Stable = 0 ☐	Falling = 1 ☐
Falling = –1 ☐	Stable = 0 ☐	Rising = 1 ☐
Falling = –1 ☐	Stable = 0 ☐	Rising = 1 ☐

3. Specific criteria

Antithrombin	Normal = –1 ☐	Low = 1 ☐
Protein C	Normal = –1 ☐	Low = 1 ☐
----------	Normal = –1 ☐	Abnormal = 1 ☐

DIC – laboratory test - summary

- **↓ platelets and ↓ fibrinogen**
- ↓ ATIII
- ↑ DD
- ↑ PT, aPTT
- ↑ schistocytes
- non-coagulant tests (organs failure)
  - ↑ creatinine, liver tests
  - ↓ pH, pO_2

DIC - treatment

- **identification and treatment of trigerring disease**
- **substitution:**
  - coagulation factors (FFP)
    - if PT or aPTT > 1,5 R
  - Fibrinogen
    - < 1 g/l
  - platelets
    - < 20 x 10^9/l, resp. 50-80 x 10^9/l and bleeding symtomes
  - nature coagulation inhibitors (ATIII < 65%, sepsis (a)PC)
- **heparin** (LMWH) in prophylactic dose
  - after bleeding cessation
- other (antifibrinolytics only in case of hyperfibrinolysis)

„DIC-like syndrom“

- MAHA
  - TTP
  - HUS
  - HELLP
- HIT/T
- cavernous hemangioma
- APS (catastrophic form)

Acquired inhibitor of FVIII

- elderly people (after pregnancy)
- incidence 1 / 1 000 0000 / year
- 50 %: autoimmune disease, malignancy, pregnancy
- 50% idiopatic
- bleeding:
  - muscles and soft tissue
  - traumatic, surgery, CNS
  - 8-22% mortality
- ↑ aPTT, in mixing test too,
- assay of inhibitor FVIII: Bethesda unit
- treatment:
  - bleeding: rFVIIa, aPCC (FEIBA)
  - eradication by immune suppression (CS, CFA, anti-CD20)

Antiphospholipid antibodies

- heterogenous auto-antibodies against proteins bound to negatively charged phospholipids on cell membranes

Antiphospholipid antibodies - mechanism

- inhibition:
  - release of prostacyclin from the endothelium
  - protein C activation
  - fibrinolysis activation by complex prekalikren+FXII
- stimulation:
  - activation of platelets
  - activation of FX on platelet surface
- other effects outside haemostasis

Antiphospholipid syndrome clinical criteria

Thrombosis:

- venous or arterial
- proven only histologically
- but not superficial thrombophlebitis

Antiphospholipid syndrome clinical criteria

Pregnancy disorders:

- three or more subsequent spontaneous abortions before the 10th week of gestation (excluding other causes)
- one or more deaths of morphologically normal fetus (documented by sonography or direct examination) after week 10 of gestation
- one or more premature births (34 weeks and earlier) of a healthy newborn in severe pre-eclampsia or severe placental insufficiency

Antiphospholipid syndrome laboratory criteria

- anticardiolipin antibodies (ACLA):
  - IgG and/or IgM > 40 U/ml or > 99. percentil)
- anti-β-glycoprotein I antibodies:
- IgG and/or IgM > 99. percentil
- are present 12 weeks or more weeks apart
- it is examined by a standardized ELISA

Antiphospholipid syndrome laboratory criteria

Lupus anticoagulans:

- are present 12 weeks or more weeks apart
- evidence of prolongation of the screening test (aPTT, PT)
- there is no correction by norma plasma
- shortening after addition of excess of phospholipids

Antiphospholipid syndrome - diagnosis

- presence of at least one criterion:
  - laboratory
  - clinical
- the symptom has a maximum distance of 5 years from laboratory criteria

Types of APS and management

- ***Type I* (venous)** – LMWH, UFH, W
- ***Type II* (arterial)** – LMWH, LD UFH, ASA, W
- ***Type III* (CNS, retinal)** – LMWH, ASA, W,
- ***Type IV* (combination)** – LMWH, LD UFH, W
- ***Type V* (abortions)** – LMWH, ASA
- ***Type VI* (no clinical criteria)**
  - – in pregnancy (ASA, LD W)
  - – in situations at risk for thrombosis (LMWH, LD UFH)