Disorders of Hemostasis

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Bleeding - classification

etiology:

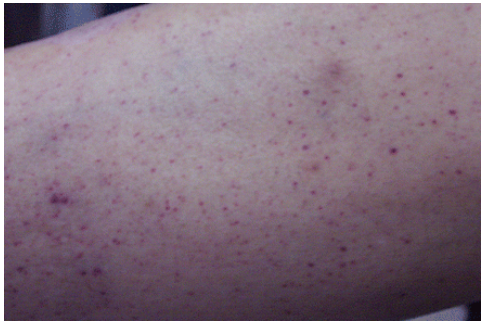
- acquired (more frequent, PT history, esp. medications) or inherited (family history).
- surgical, posttraumatic, coagulopathy, trombocytic, vascular.

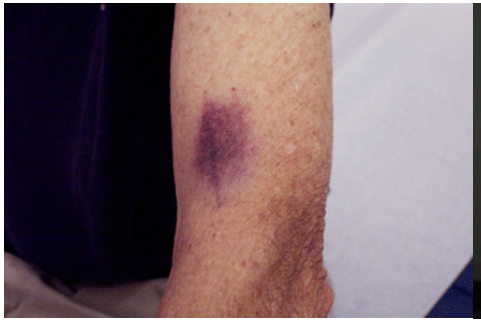
presentation:

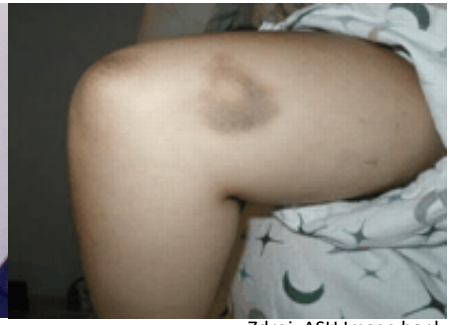
- isolated or part of a syndrome,
- mucosal or skin
- spontaneous or induced, new or repeated,
- at expected locations (menstrual)

Clinical approach

- Signs of systemic disease? (sepsis, anemia, lymfadenopathy, hepatosplenomegaly, non-hematol. sites ?)
- **Bleeding sites**: mucosa (oral cavity), skin (petechia, <1cm purpura, >1cm ecchymoses), vagina, urethra, anus, urine, stool.







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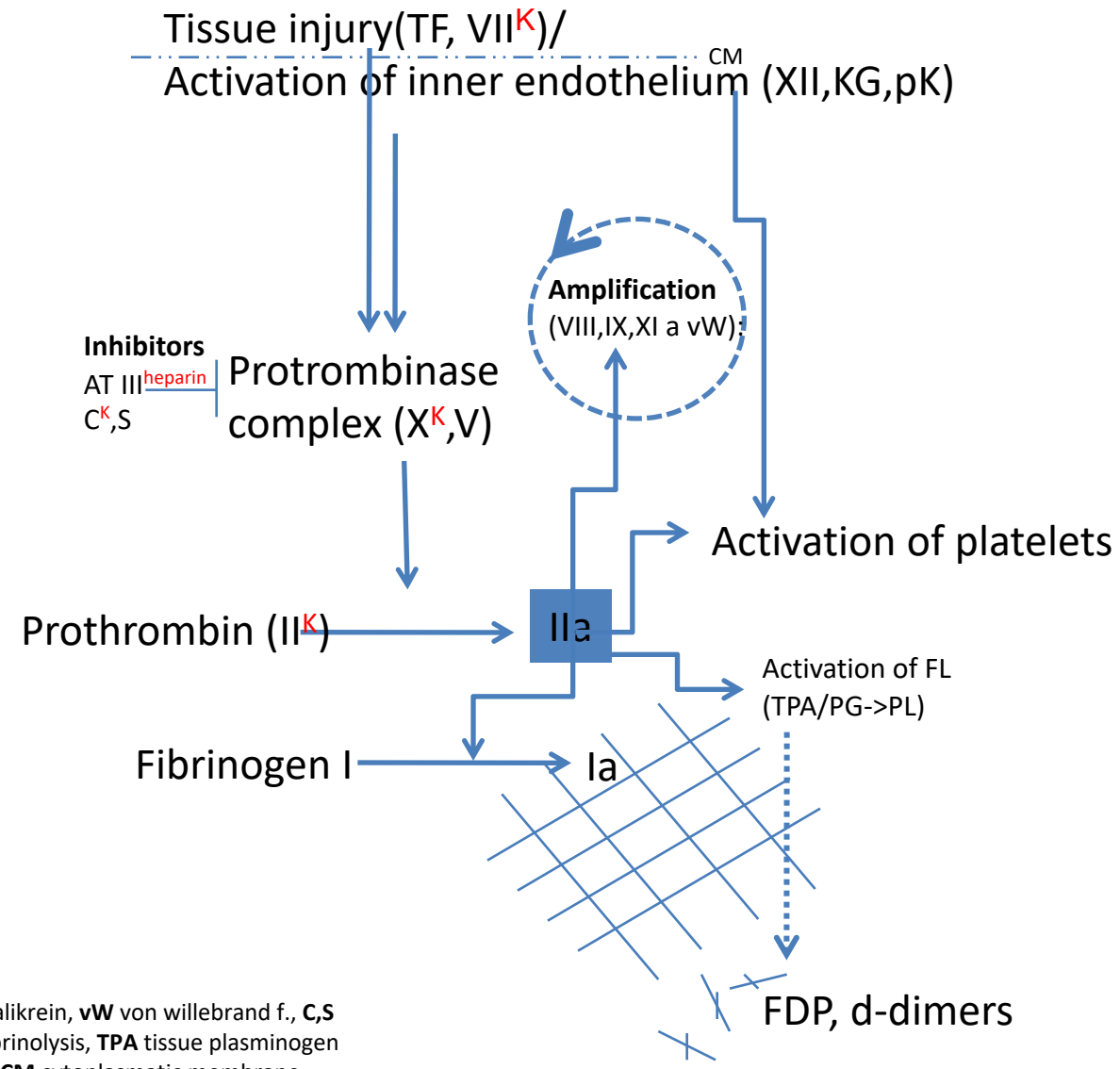
- **Laboratory tests**: blood cell count (Hgb: anemia, platelets:TCpenia), coagulation (APTT/INR). Other tests.

Laboratory approach

- **Platelets** (primary hemostasis= aggregation/adhesion)
- **Blood (plasma) coagulation factors** (secondary hemostasis=fibrin clot)
- **Inhibitors of coagulation cascade**
  (ATIII, C, S)
- **Fibrinolytic factors** (tertiary hemostasis)
  (TPA, PG, PL)

Laboratory approach

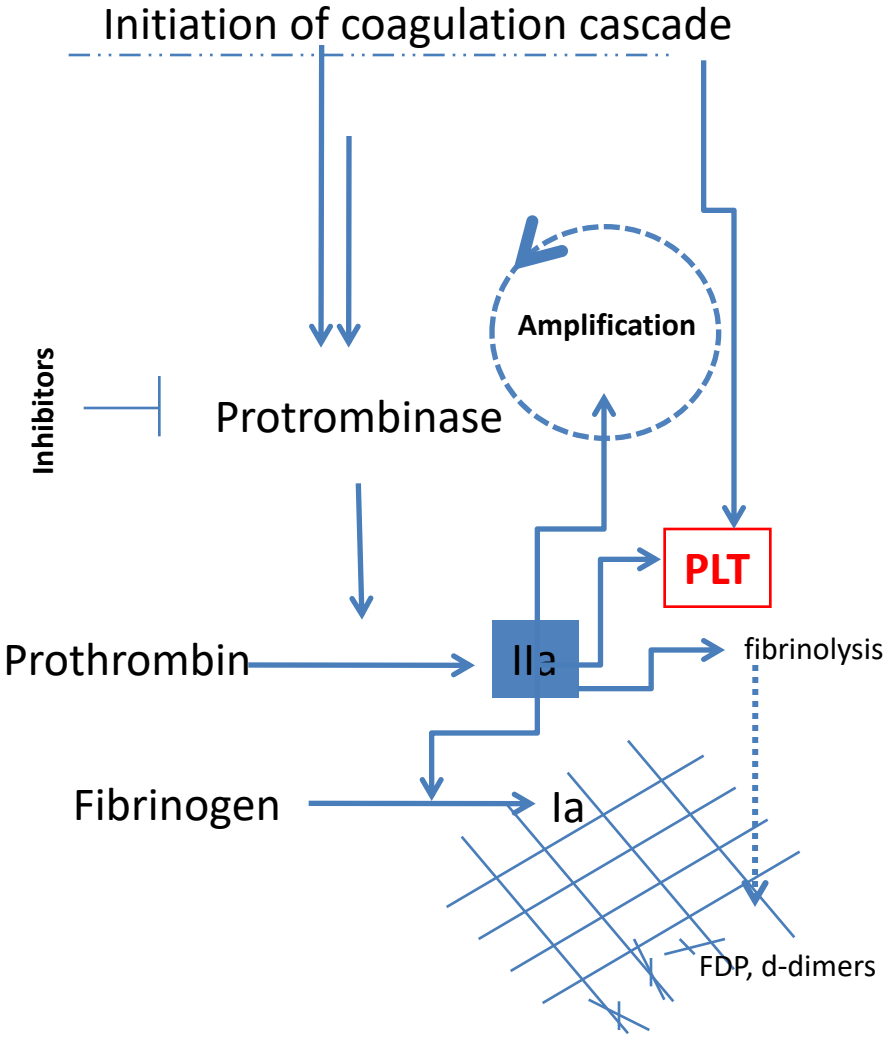


TF tissue factor, **KG** kininogen, **pK** prekalikrein, **vW** von willebrand f., **C,S** protein C,S, **ATIII** antithrombin III, **FL** fibrinolysis, **TPA** tissue plasminogen activator, **PG** plasminogen, **PL** plasmin, **CM** cytoplasmatic membrane

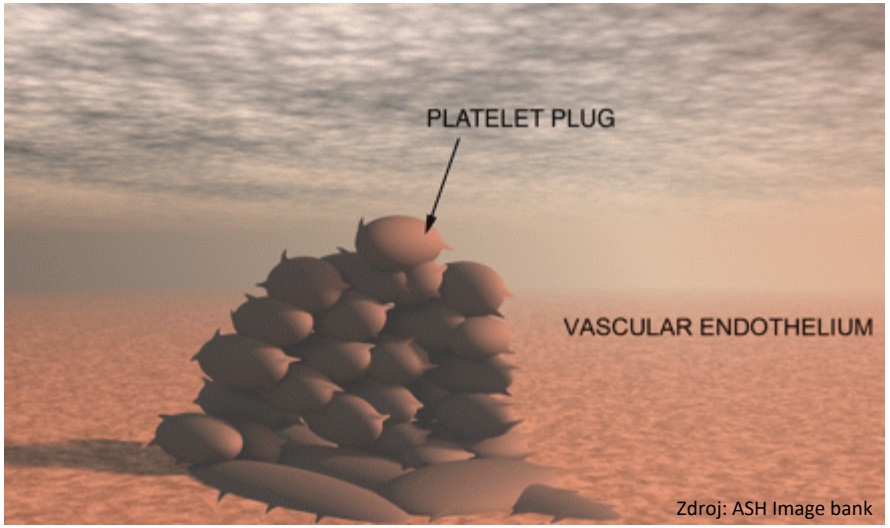
Bleeding Disorders

- Trombocytopenia/pathia
- Coagulopathy
- Vasculopathy

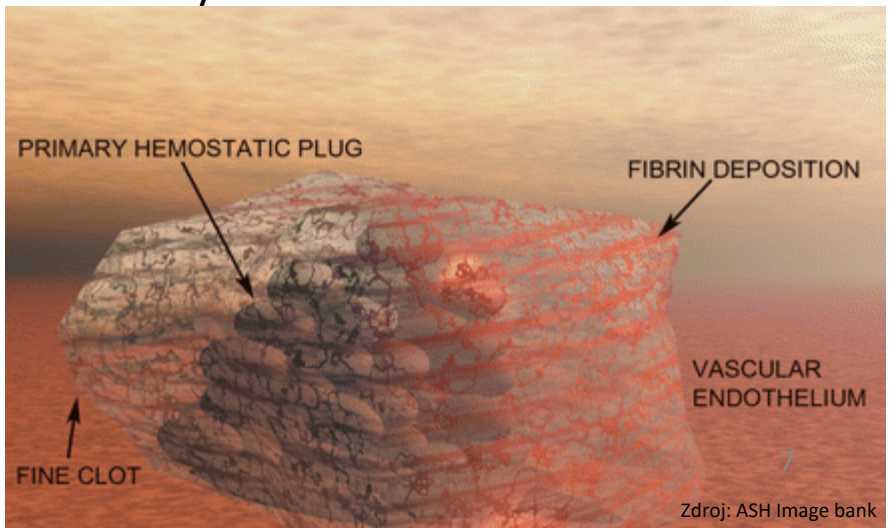
Role of platelets and endothelium



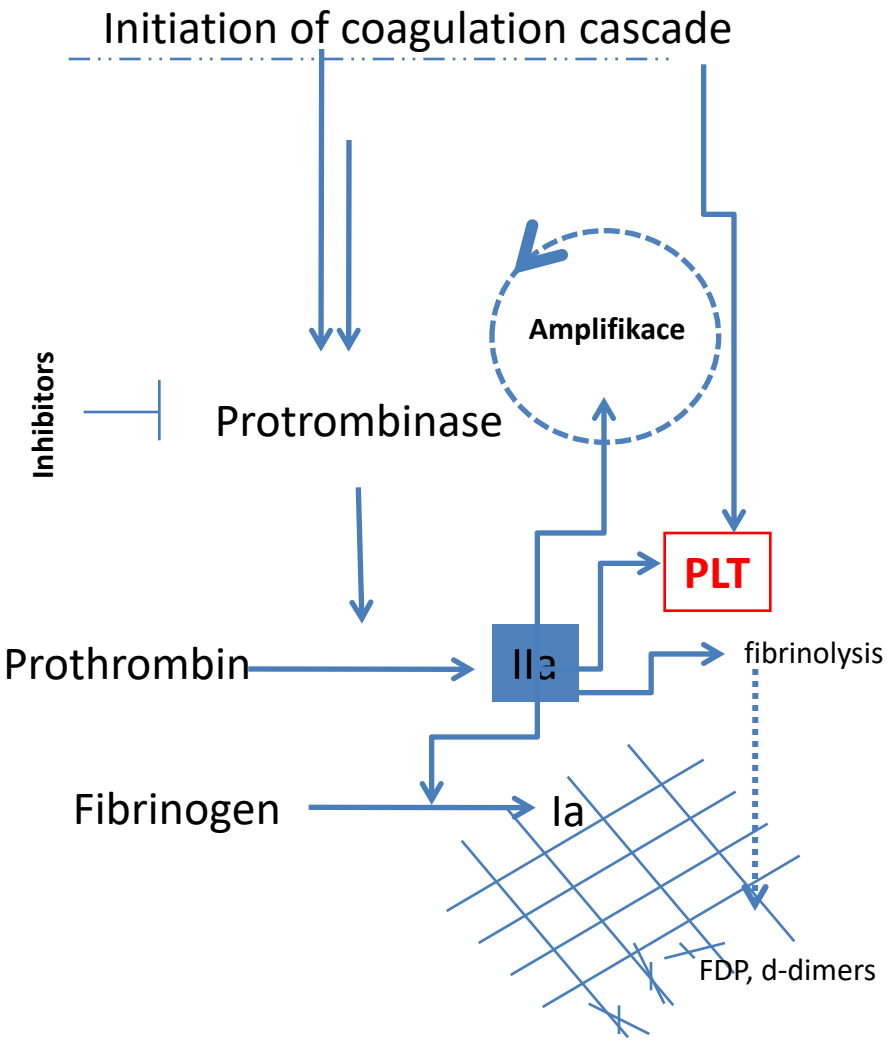
Primary hemostasis



Secondary hemostasis



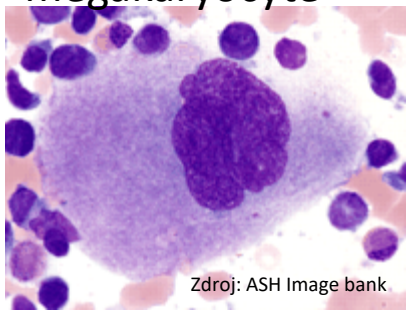
Trombocytopenia/pathia



Number: 150-450.000/uL, CAVE ~ under 20
Morphology: MPV (~ 6 fL)
Function tests: adhesion/aggregation (ADP, ristocetin)
Tests for granules: ELISA/RIA

Classification:
Quantitative : TC penia (! pseudoTCpenia)
Qualitative: TC pathia

megakaryocyte

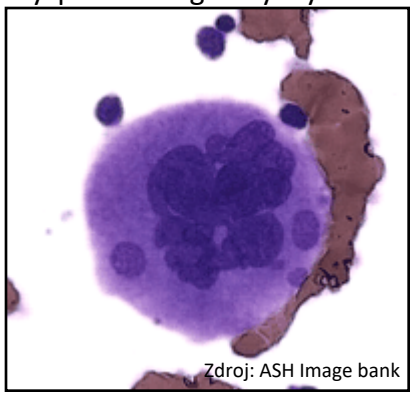


Trombocytopenia

- PG:

  1) **decreased production of PLT in BM** (aplasia, dysplasia, tumor infiltration, pharmacologic, ethylic, nutrition megaloblastic anemia, HIV a parvoviral, inherited).

Dysplastic megakaryocyte



  2) **increased destruction of PLT**:

  autoimmune (ITP, secondary to SLE,

  CLL, lymphomas), angiopathic (DIC, TTP/HUS), hypersplenism, relative(blood transfusion).

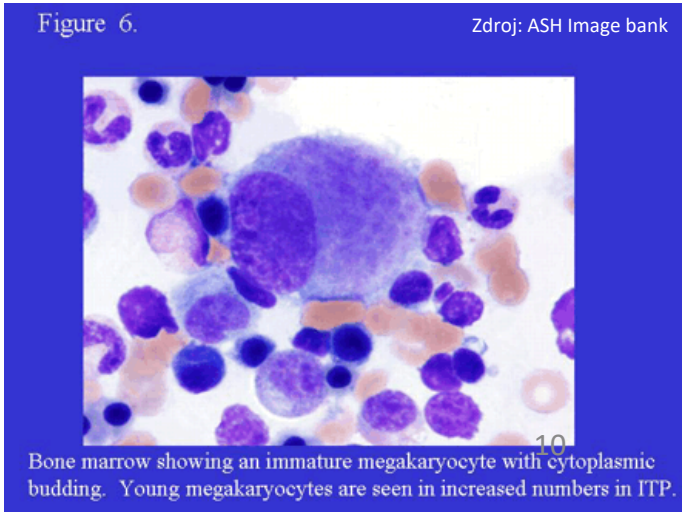
PG: patogenesis

Immune Trombocytopenic Purpura

- **PG**: IgG/IgM against GP IIb/IIIa, TC destruction
- **CL**: bleeding, chronic often relapsing, primary/secondary…..Compl.: intracranial!
- **DG**: exclusion of other possible causes (BM and PB analyses)
- **TH**: steroids, IVIg,

  Splenectomy, TPO

  other immunosuppression



PG: patogenesis, CL: clinical, DG: diagnosis, C: complication, TH:therapy

Trombocytopathy

- PG: 1) **Inherited trombocytopathy**: defect of membrane glycoprotein, loss of granules
- 2) **Acquired trombocytopathy**:
  medications (aspirin, NSAID, ATB, Heparin)
  organ failure (Liver, Kidney, DIC)
  paraneoplastic (MM, NHL, MDS, MPS)

- CL: mucosal bleeding
- DG: BT, abnormal PLT function tests
- TH: PLT transfusion (if bleeding, before surgery)

PG: patogenesis, CL: clinical, DG: diagnosis, C: complication, TH:therapy

Coagulopathy

- **Inherited:**

Hemophilia and other inherited coagulopathy

Von Willebrands disease

- **Acquired:**

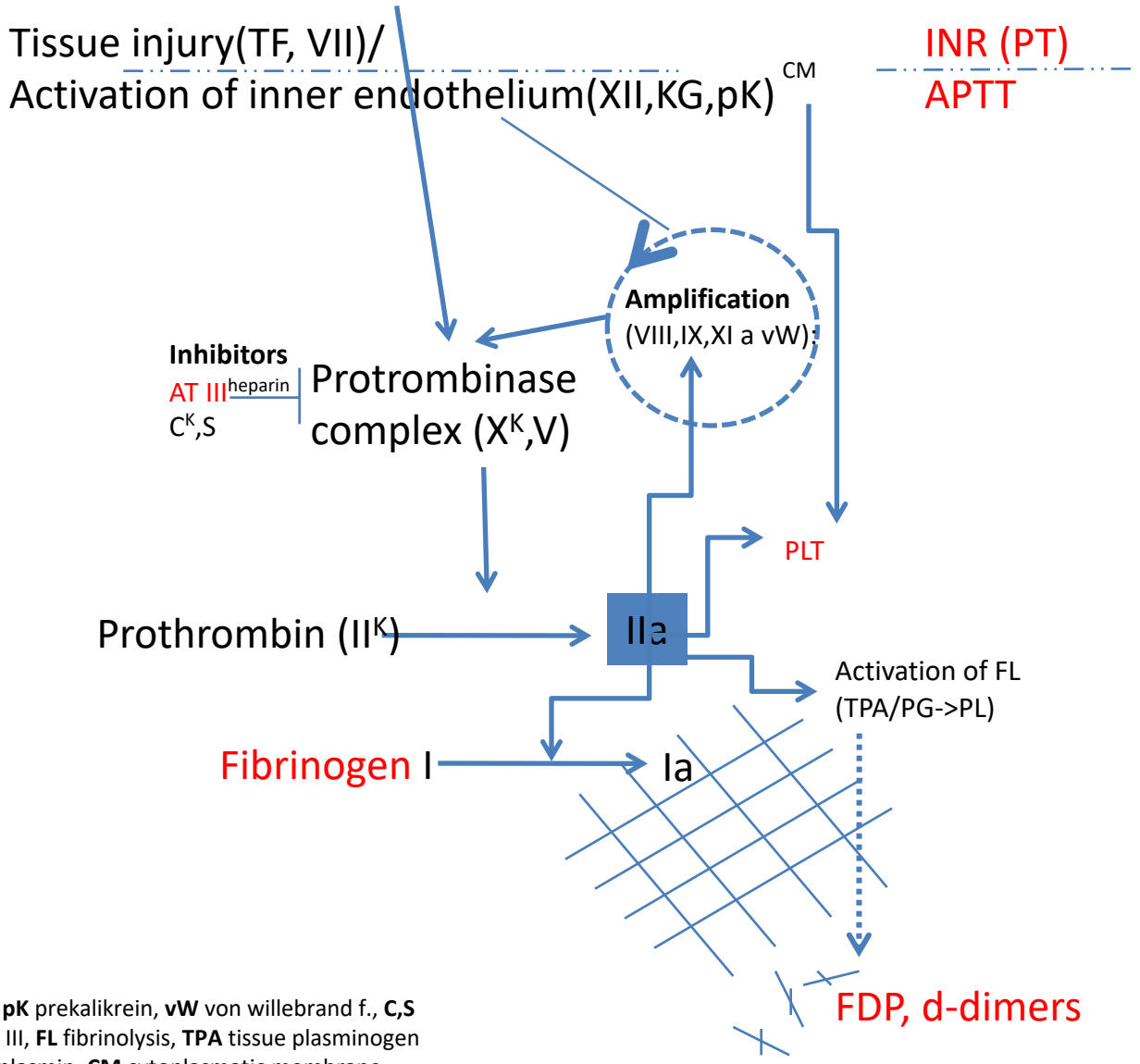
Deficiency of vit. K

Liver disease

Overdose of anticoagulants (Heparin, Warfarin)

DIC, acquired anticoagulants, massive transfusion

Laboratory approach



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Hemophilias

- **Pg**: inherited deficiency of VIII, IX, XI (<2% severe, >5% mild), 1:10.000
- **CL**: Hemarthros and other spontaneous hematomas
- **DG**: APTT prolonged, DNA Mutation, X chromosome-linked, recessive
- **C**: autoimmune (inhibitors VIII, IX), infection
- **TH**: substitution with a deficient factor
- **PR**: diagnosis at fetal age, cryoprecipitate

PG: patogenesis, CL: clinical status, DG: diagnosis, C: complications TH: therapy, PR: prevention/profylaxis

Other inherited coagulopathies

- Deficiencies: I, II, V, VII, IX, X, XII, XIII, 1:100.000
- **CL**: no spontaneous hematomas, infreq. Hypercoagulation states (XII)
- **K**: post-surgery bleeding
- **DG**: prolongation of APTT, INR, APTT/INR
- **TH**: fresh frozen plasma

- Specific defects: dysfibinogenemia (AD), afibrinogenemia (lethal-abortions)

PG: patogenesis, CL: clinical status, DG: diagnosis, C: complications TH: therapy, PR: prevention/profylaxis

Von Willebrands disease

- Deficiency of vW (partial AD/total AR), 1:5.000
- **PG**: vW multimers on endothelium and PLT bind and protect VIII, facilitate aggregation/adhesion of PLT.
- **CL**: mucosal bleeding, thrombocytopenia
- **DG**: TC analyses (agregometry-ristocetin, Imuno-, DNA-seq), prolongation of APTT, BT, decrease of VIII
- **C**: menorrhagia, bleeding following NSAID
- **TH**: administration of VIII (as in hemophilia)

PG: patogenesis, CL: clinical status, DG: diagnosis, C: complications TH: therapy, PR: prevention/profylaxis

Acquired koagulopathy – vit. K def.

- **PG**: dietary, hepatopathy, malabsorption, warfarin overdose, …
- Vit K:cofactor (γ carboxylation II, VII, IX, X, C, S)
- **DG**: prolongation PT>APTT
- **C**: 1) neonatal hemorrhagic disease
- 2) esophageal variceal bleeding (liver cirrhosis)
- **TH**: vit. K administration(10mg i.v.), FFP

PG: patogenesis, CL: clinical status, DG: diagnosis, C: complications TH: therapy, PR: prevention/profylaxis

Acquired koagulopathy - inhibitors

- **PG**: VIIIi, IXi, vWi (neutralization antibodies)
- **DG**: prolongation of APTT, dilution test with healthy plasma
- **CL**: prolonged postsurgical and posttraumatic bleeding, paraneoplasia, …
- **TH**: steroids, substitution upon bleeding

Vasculopathy

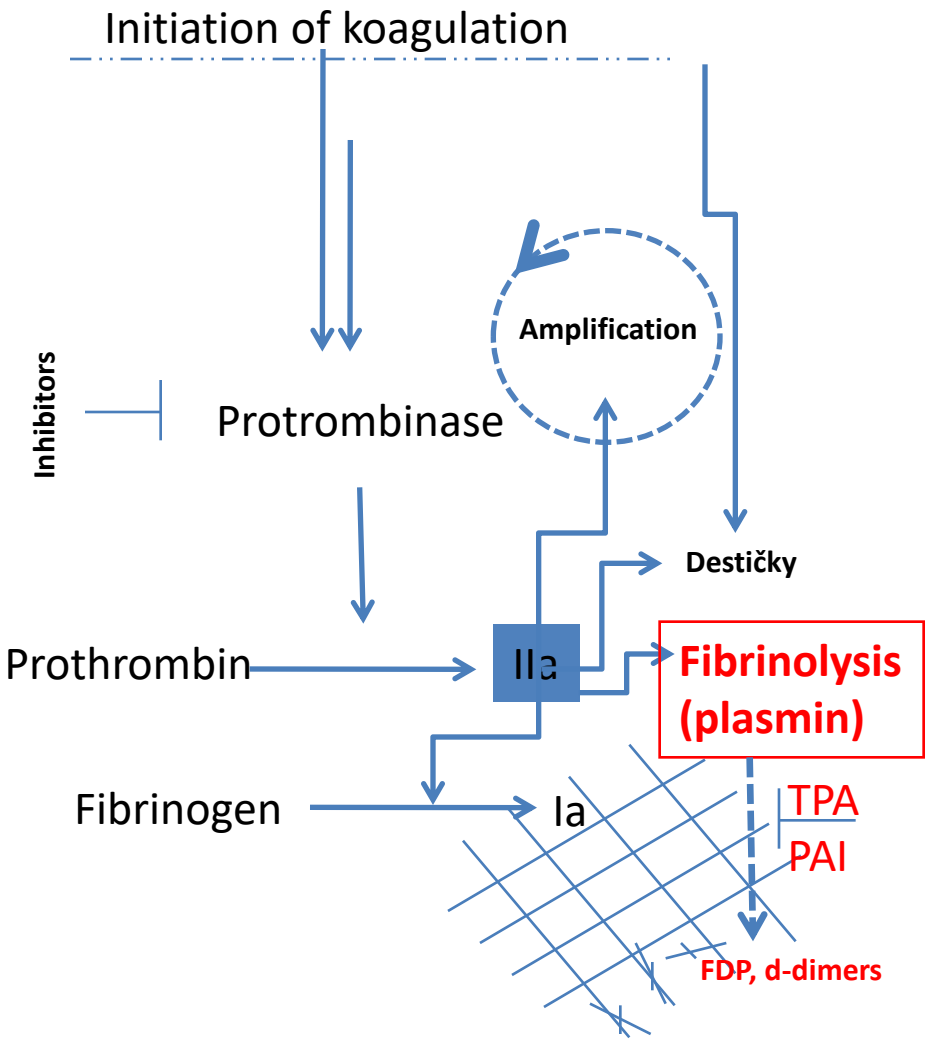
- PG: **Osler-Weber-Rendu sy** (AD, starts in adults) : abnormal structure of vessels leading to teleangiectasia.
- CL: epistaxis, Iron deficiency, menorhagia
- TH: local

- PG: **Henoch Schonlein purpura** (autoimune)
- CL: purpura lower extremities, mesenterial vasculitis, arthritis, nephritis
- TH: immunosupression

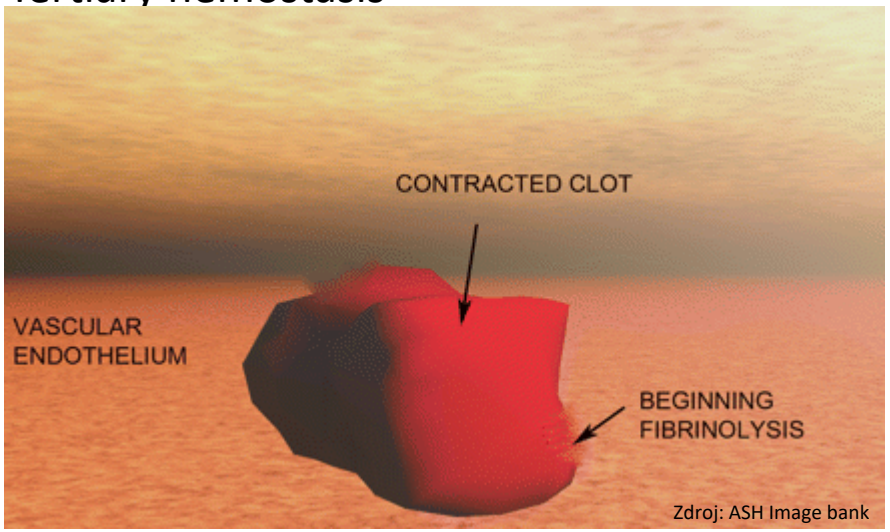
- Other: **scurvy**

PG: patogenesis, CL: clinical, DG: diagnosis, C: complication, TH:therapy

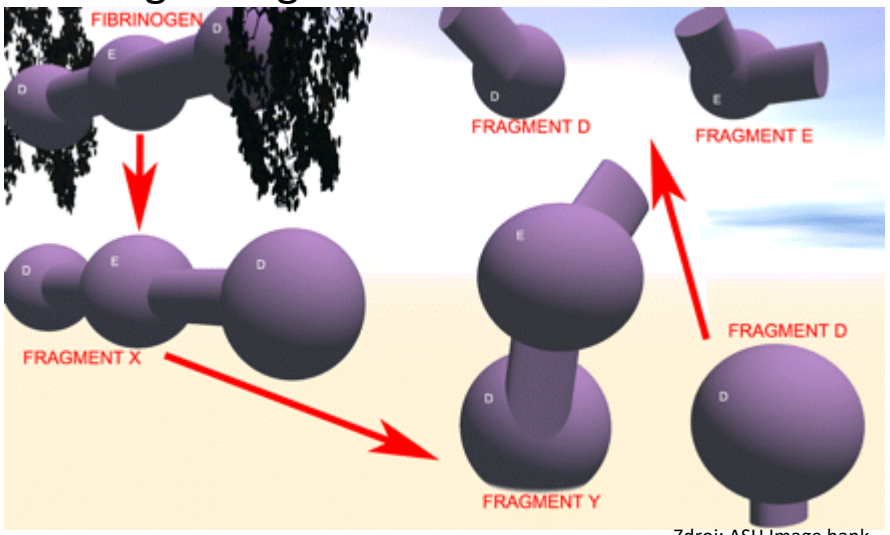
Role of fibrinolysis



Tertiary hemostasis



Fibrinogen degradation



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Failure of hemostasis : DIC

- **PG**: secondary: trauma, surgery, tumors (TF), organ failure, sepsis, shock (hyperactivation of endothelium)

- **CL**: 1.phase: activation of coagulation cascade (procoagulation state = thrombosis and organ microthrombosis), *latent period*

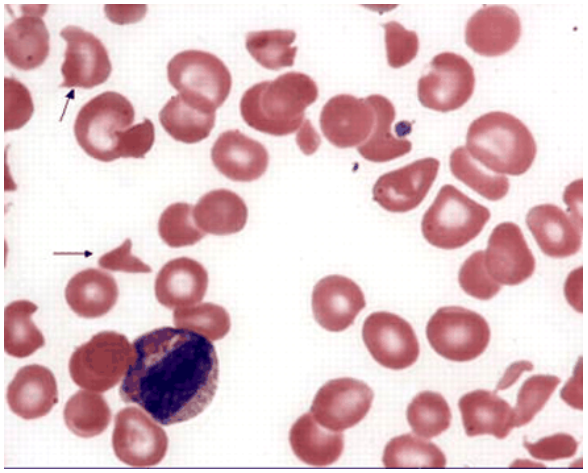
  2. phase: consumption coagulopathy = fibrinolytic bleeding, *life-threatening state*.

Failure of hemostasis : DIC

- **Acute or chronic (SIRS)**
- **thrombin hyperactivity** acute/chronic
- **hyperfibrinolysis** (tPA vs. PAI, PAI induced by SIRS) in acute DIC
- **isolated hyperfibrinolysis** (activated tPA independently on thrombin… APL?)
- Other states (gynecologic, organ failures..) combined thrombin hyperactivity/ hyperfibrinolysis (elevated d-d)

Failure of hemostasis : DIC

- **DG**: 1. faze: shortened APTT/PT, elevated d-d, decreased PLT and ATIII.
- 2. faze: prolonged APTT/PT, TT, low FBG. Schistocytes:



- **TH**: 1. faze: anticoagulation, administration of ATIII, FFP. 2. faze: FFP, PLT, FBG, ERY.

Hemorrhagic diathesis - review

- Mechanisms of blood clotting system: prim./sec./terc. hemostasis
- Disorders: Thrombocytopenia/pathy, Vasculopathy, Coagulopathy
- DIC – failure of hemostatic mechanisms

Biomedicine and Biotechnology

B02981 / B82981

Summer semester

This subject focuses on educating students in biomedical research and biotechnologies. It teaches the basis of scientific work, introduction to methodology in biomedicine up to the development of novel diagnostics and therapeutics. Lectures and seminars will contain the insight into modern tools such as transgenic biology or global technologies such as OMICs.

Lectures:

CELL BIOLOGY

CLINICAL PROTEOMICS

GENETICS

MEDICAL CHEMISTRY

*Semestr will finish with introductory visit of the Institute **BIOCEV**, First Faculty of Medicine*

Lectures will be held every other week at the
Institute of Pathological Physiology
U Nemocnice 5, Praha 2, 128 53

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