Bleeding disorders: hemophilia, von Willebrand disease

Dr. Ildikó Istenes
Semmelweis University, I. Dept. of Medicine
16th March, 2016
Roles of the hemostatic system:

- Blood remains liquid within the blood vessel
- Formation of thrombus at the site of injury (no further blood loss) and reconstruction of the vessel wall
Vessel wall damage-exposure of the subendothelium

• **Vascular constriction**: bleeding diminishes (seconds)
  
• **Primary hemostasis**:  
  – Platelet adhesion- activation-aggregation (3-5 minutes)

• **Secondary hemostasis**  
  – Clot formation- fibrin formation (10-30 minutes)  
  – fibrinolysis and reconstruction of vessel wall (days, weeks)
Thrombocyte adhesion and aggregation

Red cell

Activated platelet

Endothelium

Sub endothelium

Fib: Fibrinogen

VWF: von Willebrand Factor

Gpllb-IIIa

Fibronectin, collagen

Gpllb-IX-V

Gpllb-IIIa
Secondary hemostasis
Extrinsic tenase: VIIa, TF, PL, Ca

Intrinsic tenase: IXa, VIIIa, PL, Ca

Prothrombin time

aPTI: checks clotting from XII
PI (INR): checks clotting from VII
TI: fibrinogen – fibrin formation
Reptilase time: fibrinogen-fibrin formation (a heparin does not inhibit reptilase)

Injury

Initiation

Protrombinase Xa, Va, PL,Ca

Prothrombin (II) → Thrombin (IIa)

Enhancement and propagation

Activated partial thromboplastin time

Fibrinogen→fibrin

XIIIa : fibrin cross binding

FDP: D-dimer

clot

Plasmin stabilization
Protrombinase
Xa, Va, PL, Ca

Protrombin (II) → Trombin (IIa)

Extrinsic tenase: VIIa, TF, PL, Ca

intrinsic tenase: IXa, VIIIa, PL, Ca

TFPI

APC
IIa+ trombomodulin, Protein S

Antitrombin III

XII → XI → IX

Fibrinogen → fibrin
XIIIa fibrin cross binding

plazmin

FDP: incl. D-dimer

α 2 antiplazmin

PAI

Stabilization
Fibrin formation and fibrinolysis
Assessment of primary hemostasis

• Bleeding time: an overall assessment of primary hemostasis
  – e.g. Ivy method
  – PFA 100 – standard method

• Platelet count, function tests

• Von Willebrand factor
  – Antigene
  – Activity
  – Multimer analysis
Ivy bleeding time

- A standard-sized incision is made around 10 mm long and 1 mm deep.
- The time from when the incision is made until all bleeding has stopped is measured and is called the bleeding time.
- Every 30 seconds, filter paper or a paper towel is used to draw off the blood.
- The test is finished when bleeding has stopped completely.

- Normal values: between 3 – 10 minutes depending on the method used.
- Causes of prolonged bleeding time:
  - Disorders of the primary hemostasis
  - technical error: e.g. depth of the incision
PFA 100- Platelet Function Analyser

Method:

It aspirates blood in vitro from a blood specimen into disposable test cartridges through a microscopic aperture cut into a biologically active membrane at the end of a capillary. The membrane of the cartridges are coated with collagen and adenosin diphosphate (ADP) or collagen and epinephrine inducing a platelet plug to form which closes the aperture.

The PFA test result is dependent on platelet function, plasma von Willebrand Factor level, platelet number, and (to some extent) the hematocrit.
Assessment of secondary hemostasis

**Coagulation**
- Screening tests (+ mixing studies when necessary)
  - aPTT: checks clotting from XII
  - PT (INR): checks clotting from VII
  - TI: fibrinogen – fibrin formation
- Fibrinogen
- Factor levels
- Inhibitor levels
  - Antithrombin, Protein C, Protein S
- Activated Protein C resistance
- Lupus anticoagulant

**Fibrinolysis**
- FDP: fibrinogen degradation products
- D-dimer
- Plasminogen
- Antiplasmin
- Plasminogen activator
- Plasminogen activator inhibitor
Bleeding disorders

– Disorders of primary hemostasis
  • Vasculopathies, vasculitides
  • Thrombocytopenias and thrombocytopenopathies

– Disorders of secondary hemostasis
  • Hemophilias
  • Acquired coagulopathies

• Von Willebrand disease
## Clinical characteristics of bleeding disorders

<table>
<thead>
<tr>
<th>Clinical symptom</th>
<th>Bleeding disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical symptom</strong></td>
<td><strong>Trombocyte defect</strong></td>
</tr>
<tr>
<td>Timing of bleeding</td>
<td>Immediate (controlled by pressure)</td>
</tr>
<tr>
<td>Site of bleeding</td>
<td>Skin, mucosus membrane (oral, gastrointestinal)</td>
</tr>
<tr>
<td>Bleeding after small injuries</td>
<td>Frequent</td>
</tr>
<tr>
<td>Petechiae</td>
<td>frequent</td>
</tr>
<tr>
<td>Ecchimosos</td>
<td>Small superficial</td>
</tr>
<tr>
<td>Hemarthros</td>
<td>Rare</td>
</tr>
<tr>
<td>Muscle hematome</td>
<td>Rare</td>
</tr>
<tr>
<td>Bleeding after surgical interventions</td>
<td>Immediate, mild</td>
</tr>
<tr>
<td>Sex of the patient</td>
<td>80-90% female</td>
</tr>
<tr>
<td>Positive family history</td>
<td>rare</td>
</tr>
</tbody>
</table>
## Clinically important bleeding types

<table>
<thead>
<tr>
<th>Type</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemophilia type</td>
<td>Hemarthros, hematuria, hematoma, intramuscular bleeding</td>
</tr>
<tr>
<td>Willebrand type</td>
<td>Epistaxis, postextraction bleeding, menorrhagia, metrorrhagia, GI bleeding, mucosal bleeding</td>
</tr>
<tr>
<td>Thrombocytopenia type</td>
<td>Purpuras and hematomas together, mucosal bleeding, no hemarthros</td>
</tr>
<tr>
<td>Vascular type</td>
<td>Small skin bleedings, epistaxis, menorrhagia</td>
</tr>
</tbody>
</table>

- Hemarthros
- Hematuria
- Hematoma
- Intramuscular bleeding
- Mucosal bleedings, wet purpura
- Petechia, purpura
- Intramuscular bleeding
- Hemorrhages
Vascular disorders

• Vasculopathies (no blood vessel inflammation)
  – Hereditary:
    • hemorrhagic teleangiectasia (Osler-Weber-Rendu disease), Haemangioma, teleangiectasia (Kassabach-Merritt, von Hippel Lindau, ataxia teleangiectatica...)
  – Acquired:
    • skorbut, purpura senile, psichogen purpura, diabetes, uraemia, liver disease associated, drug induced

• Vasculitides
  – Large vessels: arteritis temporalis, Takayasu
  – Medium vessels: polyarteritis nodosa, Kawasaki
  – Small vessels: Wegener, Churg Strauss, Schönlein Henoch, microscopic polyangitis
Thrombocytopenia

- Platelet count below 150G/l
- Risk of bleeding:
  - <50G/l spontaneous bleeding which requires treatment
  - <10G/l spontaneous life threatening bleeding
Etiology of thrombocytopenia

1. Pseudothrombocytopenia:
   - EDTA induced aggregation/agglutination
   - Satellite formation between leukocytes and thrombocytes

2. Real thrombocytopenia
   - Decreased production
   - Increased destruction
   - Increase storage in spleen
## Etiology of real thrombocytopenias

### I. Decreased formation and maturation

<table>
<thead>
<tr>
<th>Bone marrow: Megakaryocyte number is low or absent</th>
<th>1. Hereditary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pl. Fanconi anaemia, Wiskott-Aldrich sy, Bernard-Soulier sy,</td>
<td></td>
</tr>
<tr>
<td>2. Acquired</td>
<td></td>
</tr>
<tr>
<td>Bone marrow damage:</td>
<td></td>
</tr>
<tr>
<td>- drugs (kemoth),</td>
<td></td>
</tr>
<tr>
<td>- Chemicals,</td>
<td></td>
</tr>
<tr>
<td>- radiation,</td>
<td></td>
</tr>
<tr>
<td>- infections</td>
<td></td>
</tr>
<tr>
<td>Bone marrow infiltration:</td>
<td></td>
</tr>
<tr>
<td>- leukaemia, lymphoma,</td>
<td></td>
</tr>
<tr>
<td>- carcinoma</td>
<td></td>
</tr>
<tr>
<td>Myelodysplasia, myelofibrosis</td>
<td></td>
</tr>
<tr>
<td>Vitamin deficiency (disturbed maturation)</td>
<td></td>
</tr>
<tr>
<td>B12 deficiency, folic acid deficiency</td>
<td></td>
</tr>
</tbody>
</table>
### Etiology of real thrombocytopenias

<table>
<thead>
<tr>
<th>II. Increased damage</th>
<th>1. Immun thrombocytopenias</th>
<th>2. Microangiopathic</th>
<th>3. Other:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marros: Megakariocyte number is normal or elevated</td>
<td>Autoimmun</td>
<td>Primary:</td>
<td>Valve implantation (mechanic), Extracorporal circulation (surface)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Acute and</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Adult chronic ITP (Idiopathic/immun thrombocytopenic purpura)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>secondary:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- drugs (co-trimoxazol, chinidin, HIT),</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- infection (HIV, H.pylori),</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- autoimmune disease(SLE),</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Malignancy (lymphoma)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alloimmun</td>
<td>Posttransfusional purpura</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Disseminated intravascular coagulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Thrombotikus thrombocytopenic purpura</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Hemolytic uraemic syndrome</td>
</tr>
</tbody>
</table>
### Etiology of real thrombocytopenias

#### III. Increased storage in spleen

<table>
<thead>
<tr>
<th>Bone marrow: The number of megakaryocytes depend on the underlying disease</th>
<th>Portal hypertension (liver cirrhosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloproliferative, lymphoproliferative neoplasms</td>
<td></td>
</tr>
<tr>
<td>Storage diseases</td>
<td></td>
</tr>
<tr>
<td>Platelet count (x $10^9$/L)</td>
<td>Risk of bleeding</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td>&gt;100</td>
<td>asymptomatic</td>
</tr>
<tr>
<td>50-100</td>
<td>invasive intervention</td>
</tr>
<tr>
<td>10-50</td>
<td>Purpura, haematoma</td>
</tr>
<tr>
<td>&lt;10</td>
<td>Spontaneous severe bleeding</td>
</tr>
</tbody>
</table>
Indication of platelet transfusion

• **Therapeutic supportation:**
  • Bleeding due to thrombopenia or thrombopathia („wet purpuras”, internal bleeding)

• **Preventive supportation:**
  • By critical platelet count (no bleeding)

<table>
<thead>
<tr>
<th>Preventive supportation</th>
<th>Plt count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable patient without fever:</td>
<td>&lt; 5-10G/l</td>
</tr>
<tr>
<td>Accompanying fever, sepsis, DIC, severe anaemia, extreme leukocytosis, progressive thrombopenia</td>
<td>&lt; 20G/l</td>
</tr>
<tr>
<td>Lumbalpunction, intrathecalis chemoth</td>
<td>&lt; 30G/l</td>
</tr>
<tr>
<td>Surgera, invasive diagnostic intervention (except for sternum punction, crista biopsy)</td>
<td>&lt; 50G/l</td>
</tr>
<tr>
<td>Neurosurgery, eye surgery, polytraumatised patient</td>
<td>&lt; 100G/l</td>
</tr>
</tbody>
</table>
VON WILLEBRAND DISEASE
Role of vWF- primary hemostasis

At high shear stress + binds and stabilizes FVIII

AGGREGATION

ADHESION

Subendothelial Collagen Receptors Exposed at Injury Site

Endothelium
von Willebrand factor

- **Produced/stored/secreted by**
  - Endothel cells
  - Megakaryocytes

- **Structure:**
  - High molecule weight multimer glycoprotein (HMWM) (dimers-multimers)
  - ADAMTS13 regulates the size of the multimer
  - Binding sites:
    - FVIII, heparin, GPIb, GPIIb/IIIa, collagen

- **Function:**
  - primary hemostasis
    - Key role in the adhesion of platelets to the injured wall
    - Aggregation
  - Binds and stabilizes FVIII

- **Its level is increased by**
  - Stress, pregnancy, oral contraceptives, DIC, chronic liver disease, hepatocellular cc., hyperthyreosis (decreased in hypothyreosis), blood group AB
  - Blood group AB
In von Willebrand disease:
The vWF is either:
- not enough
- not functioning properly (e.g. there are no large multimers)
Von Willebrand disease

• Hereditary form:
  – 1926: Erik Adolf von Willebrand, 1933: Rudolf Jürgens described it
  – 1/10000 (with symptoms), otherwise 1:100
  – This is the most frequent mild- mid-severe bleeding disorder.

• Acquired form
  – First described in 1968 (accompanying SLE)
  – Rare, exact prevalence is not known

• Characteristics:
  – vW type bleeding: Epistaxis, postextraction bleeding, menorrhagia, metrorrhagia, GI bleeding, mucosal bleeding
  – Autosomal inheritance (if hereditary)
  – Labor: bleeding time increased, abnormal aggregation to ristocetin
  – Platelet aggregation inhibitors, NSAIDs may provoke the symptoms of the illness
In 1924, a 5-year-old girl who lived on the Aland Islands was brought to Deaconess Hospital in Helsinki, Finland, where she was seen by Dr. Erik von Willebrand. It turned out that four out of 12 children of her family died of uncontrollable bleeding. This made him curious, he went to the island to make further studies. He ultimately assessed 66 members of her family and reported in 1926 that this was a previously undescribed bleeding disorder that differed from hemophilia. He recognized that:

- The autosomal inheritance pattern
- Mucocutaneous bleeding,
- Normal clotting time
- Prolonged bleeding time

He subsequently found that blood transfusions were useful not only to correct the anemia but also to control bleeding.

Variant forms of vWF disease were recognized in the 1970s, and we now recognize that these variations are the result of synthesis of an abnormal protein.
Inheritance

von Willebrand Disease Types I & II
inherited in an autosomal dominant pattern

von Willebrand disease type III
(and sometimes II) is inherited in an autosomal recessive pattern.

Unaffected “Carrier” Father

Unaffected “Carrier” Mother

Unaffected 1 in 4 chance
Unaffected “Carrier” 2 in 4 chance
Affected 1 in 4 chance

U.S. National Library of Medicine
## Types of inherited vWD

<table>
<thead>
<tr>
<th>Type</th>
<th>Characteristics</th>
<th>Clinical symptoms</th>
</tr>
</thead>
</table>
| 1    | Partial absence of vWF, **quantitative** problem | Mucosal bleedings:  
- epistaxis,  
- Postextractional bleeding  
- Gastrointestinal bleeding  
- Menorrhagia, metrorrhagia  
(hematuria is rare, purpura is not found) |
| 2    | **qualitative** problem | |
| 2A   | **Decreased vWF dependent platelet adhesion** (GPIb), with selective absence of HMWM | |
| 2B   | **Increased affinity of vWF to** the GPIb receptor of the platelet | |
| 2M   | **Decreased vWF dependent platelet adhesion** (GPIb), without selective absence of HMWM | |
| 2N   |Markedly decreased FVIII binding, no absence of HMWM | The above mentioned ones plus:  
- Articular (coagulopathic) bleeding can occur |
| 3    |Complete absence of vWF | |
| Platelet type | Thrombocytopenia- the GPIb of the platelet is dysfunctioning-enhanced adhesion | |
Acquired vWD- accompanying diseases

• Lymphoproliferative disorders:
  – MGUS, MM, WM, NHL, CLL, HSL, ALL
• Myeloproliferative disorders
  – ET, PV, CML
  In case of plt >1500G/l, there is a-vWD, therefore CAVE: Aspirin
• Solid tumors:
  – Wilms tumor, Ewing sarcoma
• Immun:
  – SLE, egyéb, GVHD
• Infekció:
  – EBV

• Kardiovascular
  – malformations
  – VSD, ASD, AS, mitral prolapsus, angiodysplasia
  – Ventricular assisted device
  – CABG
• drugs
  – (cipro/levofloxacin, cefotaxim, valproát, HES)
• Other systemic diseases:
  – Hypothyreosis, diabetes, uraemia, hemoglobinopathy, sarcoidosis, telenangiectasia, colitis ulcerosa

inactivated by antibody
Absorbed on Malignant cells
High shear stress
vWD- diagnose

• **Symptoms:**
  – mild- to moderate mucosa type bleeding, starting at any age

• **Lab tests:**
  – Screening: aPTI, plt count, PFA100, (bleeding time)
  – Specific tests vWF:Ag, vWF:Rco, vWF:CB, VIIIIF, RIPA, plasma vWF multimer analysis, vWF FVIII binding ability

• **DD:**
  – Thrombocytopenias
  – mild hemophilia
  – Aspirin treatment
vWD treatment

- Desmopressin (DDAVP, Octostim inj)
  - Synthetic vasopressin derivate that liberates vWF from endothel
  - Indicated: type 1 (it is ineffective in Type 3, and is contraindicated in type 2B, because it causes hyperaggregation which further deteriorates thrombocytopenia

- Virus inactivated FVIII/vWF concentrate (Haemate P) +/- Thrombocyta cc

- other:
  - Tranexam acid (Exacyl, antifibrinolytic), CAVE: bleeding in the urine tract
  - Contraceptives (Norcolut, in case of severe menorrhagia)
  - Avoid medication with bleeding potential
COAGULOPATHIES
History of hemophilia

• 2nd century AD.: Rabbi Juda writes that **those boys who had two brothers who previously died of circumcision, don’t have to be circumcised**.

• 12th century: Maimonides (1135-1204) (jewish doctor and philosopher) ads to this, that in this case the boy doesn’t have to circumcised **even if the deceased brothers are from different fathers**.

• 10th century : Abucalsis (moron surgeon writes )down the main characteristics of hemophilia: he **described families whose males died of bleeding after only minor traumas**

• In 1803, Dr. John Conrad Otto, a Philadelphian physician, wrote an account about "a hemorrhagic disposition existing in certain families" in which he called the affected males "bleeders". He recognised that the disorder was hereditary and that it affected mostly males and was passed down by healthy females.

• In 1937, Patek and Taylor, two doctors from Harvard, discovered anti-haemophilic globulin.

• In 1947, Pavlosky, a doctor from Buenos Aires, found haemophilia A and haemophilia B to be separate diseases by doing a lab test. This test was done by transferring the blood of one haemophiliac to another haemophiliac. The fact that this corrected the clotting problem showed that there was more than one form of haemophilia.
Hemophila B- a Royal disease

Affected man
Carrier woman

Empress Victoria
Alice
Leopold
Beatrice
Alexandra
Alexej Tsarevich
Epidemiology

Frequent hemophilias

• Hemophilia A: Factor VIII deficiency
  – 1 in 5000 male births

• Hemophilia B: Factor IX deficiency
  – 1 in 30000 male birth

Rare hemophilias:

• Deficiency of factors other than FVIII-IX
  – E.g. hemophilia C: Factor XI deficiency
    • common in Jews of Ashkenazi, otherwise rare)
Genetics - hemophilia A,B

• X-linked

• Mutation:
  – Point mutation:
    • Non-sense: severe hemophilia
    • Missense: mild- moderately severe hemophilia
  – Deletion:
    • Severe hemophilia

• Hemophilia A:
  – Intron 22 inversion is common among severe hemophilia A

• Hemophilia B:
  – There is no characteristic mutation type
  – One third is new mutation (with no family history)
Haemophilia type bleedings

- 90% of bleeding is musculoskeletal bleeding: 30% muscle hematoma, 70% hemarthros

hemarthros

hematoma

Intramuscular bleeding

Pseudotumor
Laboratory results

- Bleeding time, platelet function: **normal**
- Coagulation tests: **prolonged**
  - Protrombin time: VII, X, II, V, fibrinogen
  - Thrombin time: fibrin
  - Activated partial thromboplastin time: XII, XI, IX, X, VIII, V, II
- Mixing studies
- Tests for vWD

**Diff dg:**
- vWD Type 3, 2N
- Acquired coagulopathies:
  (vitamin K deficiency
- Inhibitory hemophilia
## Severity

### Hemophilia A, B

<table>
<thead>
<tr>
<th>Grade</th>
<th>Factor level</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>&lt;1%</td>
<td>Spontaneous bleedings: muscle, joint</td>
</tr>
<tr>
<td>Moderate</td>
<td>1-5%</td>
<td>Sponaneous bleedings are rare, severe bleedings to trauma and surgery</td>
</tr>
<tr>
<td>mild</td>
<td>5-40%</td>
<td>Severe bleeding after big trauma and surgery</td>
</tr>
</tbody>
</table>

- Factor levels remain stable throughout life and in the family
- Carrier females can have symptoms as well (due to lyonisation- inactivation of X chromosome)

### Other factor deficiencies

- Severe bleeding is less frequent (compared to A, B)
- It manifests usually after surgery, trauma, childbirth
- Factor level and the severity of bleeding do not correlate to each other
Complications

Bleeding related

• Arthropathy-disability
  – Synovitis, target joints with recurrent bleeding, contractures

• Compartment syndrome:
  – Volkmann contracture, n. femoralis lesion, quadriceps atrophy, n. peroneus atrophy

• Haemophiliac pseudotumor:
  – bone and soft tissue destruction

• Airway obstruction:
  – retropharyngeal, sublingual bleeding

• Intracranial hemorrhage

• Iron deficiency anaemia

Treatment related

• Side effects of factor suppl.
  – Urticaria, fever, sweating, palpitation

• Transfusion transmitted infection:
  – HCV, HIV

• Alloantibodies (inhibitors) against factor supplementation
Pathogenesis of Hemophilic Arthropathy

Recurrent joint bleeds (“target joints”)
- Influx of inflammatory cells (e.g., neutrophils)

Synovial hypertrophy
- Hemosiderin deposition in phagocytic cells
- Release of toxins (e.g., collagenases, proteases)

Destruction
- Cartilage
- Bone


TABLE 1
STAGES OF HEMOPHILIC ARTHROPATHY

Stage I: No skeletal abnormalities on x-ray. Soft tissue swelling caused by hemarthrosis.

Stage II: Subacute hemophilic arthropathy. Epiphyseal osteoporosis and overgrowth. No loss of cartilage space. No cysts.

Stage III: Disorganization of joint with epiphyseal irregularity. Cartilage space preserved. Subchondral cysts. Squaring and overgrowth of patella. Widening of intercondylar notch. Final stage at which process may be reversible.

Stage IV: Cartilage destruction. Joint space narrowing. Further disorganization.

Treatment

General recommendations:
- Avoid drugs with bleeding potential (aspirin, NSAID)
- Avoid sports with high risk for trauma (e.g. wrestling, boxing)
- Avoid im. Injection, use thin needle (23-25G)
- Regular exercise is recommended to strengthen muscles around joints

In case of bleeding

I. RICE
   - Rest, Ice, Compression, Elevation

II: Factor supplementation !!
   - FVIII, FIX concentrate, recombinant FVII, Protrombin complex conc (PCC), activated PCC, FFP

III. Supportive treatment
   - Fibrinolysis inhibitors (e.g. tranexam acid, CAVE: urinary tract bleedings)
   - DDAVP (desmopressin: synthetic ADH): releases vWF from endothels)
   - Pain killers (paracetamol, acetaminophen)
   - Antibiotics if necessary
   - Physiotherapy
Factor supplementation

• On-demand – start within 2 hours!
  – Target factor level:
    • Hemarthros: 25%
    • Soft tissue, GI bleeding: 50-60%
    • CNS bleeding, surgery: 100%

• Prophylactic – it has proven to be cost effective
  – factor level should not fall below 2 %
  – 2-3 times per week
  – Types:
    • Primary: after the first bleeding under 2 years, or without bleeding under 2 years
    • Secondary: recurrent, frequent bleeding above 2 years
    • Tertiary: in case of arthropathy
    • Permanent-transient

• Home treatment is possible (in Hungary since 1999)
Alloantibodies against factor

- 30% (!) of hemophilia A, and 3-8% in hemophilia B
- Usually within 50 exposition day
- Risks: Severe hemophilia, intensive, high dose substitution with FVIII
- Signs: Bleeding pattern changes
  - (large sc, im. Hematomas, GI bleedings, hematuria- similar to acquired hemophilia)
- Diagnose:
  - Mixing studies (Bethesda Unit: 1 BU inactivates the 50% of normal plasma factor)
  - Recovery is not enough (it has to be measured regularly)
- treatment
Treatment of inhibitory hemophilia

• Stop bleeding with:
  – Recombinant FVII or
  – FEIBA: Factor Eight Inhibitor Bypassing Activity
    (=activated prothrombin complex concentrate, contains: IIa, Xa, VII, IX, Protein C, S)

• Immuntolerance induction:
  – High dose of factor
<table>
<thead>
<tr>
<th>Factor</th>
<th>Symptoms</th>
<th>which test is abnormal</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>VII</td>
<td>Mucosal bleeding, muscle, joint bleeding</td>
<td>PI</td>
<td>FVII</td>
</tr>
<tr>
<td>V</td>
<td>Mucosal bleeding</td>
<td>PI, aPTI</td>
<td>FFP, rFVIIa</td>
</tr>
<tr>
<td>X</td>
<td>Umbilical cord, muscle, joint</td>
<td>PI, aPTI</td>
<td>FFP, PCC, rFVIIa</td>
</tr>
<tr>
<td>XI</td>
<td>Posttraumatic bleeding</td>
<td>aPTI</td>
<td>FFP</td>
</tr>
<tr>
<td>XIII</td>
<td>Umbilical cord, intracranial, joint, <strong>habitual abortus</strong></td>
<td>none</td>
<td>FXIII, FFP</td>
</tr>
<tr>
<td>I</td>
<td>Umbilical cord, muscle, joint, <strong>habitual abortus</strong></td>
<td>aPTI, TI, PI, Reptil time</td>
<td>fibrinogen cc, FFP</td>
</tr>
<tr>
<td>II</td>
<td>Umbilical cord, muscle, joint</td>
<td>PI, aPTI</td>
<td>FFP, PCC</td>
</tr>
<tr>
<td>XII</td>
<td>Thrombosis!, <strong>habitual abortus</strong>, AMI (activates fibrinolysis)</td>
<td>aPTI</td>
<td>--</td>
</tr>
</tbody>
</table>

FFP: fresh frozen plasm, PCC: protrombin complex concentrate
Acquired coagulopathies

• Deficiency of vitamin K dependent factors (II, VII, IX, X, protein C, S)
  – Neonatal hemorrhagic disease, biliary obstruction, insufficient vitamin K absorption, vitamin K antagonist treatment, liver disease

• Nephrotic syndrome:
  – FIX, XIII, At III loss through proteinuria

• **Acquired hemophilia**

• Massive transfusion syndrome

• Disseminated intravascular coagulation
Acquired inhibitory hemophilia

- 0.2-1.5/1000000: between 60-80 ys (smaller peak: 20-30 ys, female, after delivery)
- Usually autoantibodies against FVIII
- 50% associated with disease (malignant, autoimmune, infection HBV, HCV, drugs, pregnancy), 50% idiopathic
- Dg: aPTT prolonged + mixing studies
- Clinical features:
  - Bleeding with negative family history
  - Suffusions, big hematomas, mucosal bleedings (no joint bleeds!)
- Treatment:
  - Bleeding: bypassing agent, (plasmapheresis, immunadsoroption)
  - Steroid- cyclofosfamid- Factor VIII
Case 1-

A 1-year-old boy is brought to your clinic. Developmentally normal, his parents had noticed him to be bruising easily. Family history is negative.

Coagulation tests show:

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>13s</td>
<td>11-14s</td>
</tr>
<tr>
<td>aPTT</td>
<td>105s</td>
<td>23-35s</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>2,7g/l</td>
<td>1,5-4g/l</td>
</tr>
<tr>
<td>Trombin time</td>
<td>13s</td>
<td>10-13s</td>
</tr>
</tbody>
</table>

What is the first step?:
- Repeat test to confirm abnormality and exclude lab error
- Mixing studies to exclue/verify the presence of inhibitors

Mixing with normal plasma corrects abnormal aPTT

Which factors would you measure?
**Prothrombin time**

**Extrinsic tenase:** VIIa, TF, PL, Ca

**Intrinsic tenase:** IXa, VIIIa, PL, Ca

**Check:** Factor VIII, IX, XI (! FXII deficiency is not associated with bleeding)

**Protrombinase**

Xa, Va, PL, Ca

**Prothrombin (II) →Thrombin (IIa)**

**Fibrinogen→fibrin**

**XIIIa fibrin cross binding**

**Activated partial thromboplastin time**

**XII →XI→ IX**

**aPTI:** checks clotting from XII

**PI (INR):** checks clotting from VII

**TI:** fibrinogen – fibrin formation

**Reptilase time:** fibrinogén-fibrin formation (a heparin does not inhibit reptilase)

**Stable clot**
The tests are repeatedly abnormal

- his FIX and FXI assays are normal but the FVIII assay is <1 IU/dl.

- Diagnose: severe Haemophilia A

- Treatment: start prophylaxis e.g after the first intraarticular bleeding
If this patient is a girl (with FVIII def)?

- Differential diagnose?
  - vWD: Severe Type 1 or Type 3, or Type 2N
    - Bleeding time/PFA 100 should be abnormal
    - vWF assays should be abnormal

- If vWF assays are normal, how could a girl have haemophilia A?
  - Carrier mother and hemophiliac father
    - Family history should be positive
  - There is only one X chromosome
    - Turner syndrome: X0 or
    - Androgen insensitivity: patient is XY, but fenotypically female
      Kariotype should be performed
  - Extreme lyonisation of the X chromosome
    - inactivation of one X chromosome due to the mutation of Xist gene, which is responsible for the process
Case 2

• A 45-year-old man presents with an extensive above knee DVT extending into the iliac veins. He is otherwise well with no past medical history of note.

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>14s</td>
<td>11-14s</td>
</tr>
<tr>
<td>aPTT</td>
<td>&gt;120s</td>
<td>23-35s</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>3.2g/l</td>
<td>1.5-4g/l</td>
</tr>
<tr>
<td>Trombin time</td>
<td>13s</td>
<td>10-13s</td>
</tr>
</tbody>
</table>
Possible explanations for prolonged aPTT?

- Hereditary bleeding disorder?
  - Probably not: age, no previous health problems, no bleeding (!but it is not impossible for a hemofiliac to have DVT!)

- APL?
  - NO: the prolonged APTT corrects in a mix with normal plasma.

- XII deficiency?
  - YES: Factor XII:C <1%
  - ! Factor XII can activate fibrinolysis and a deficiency may, therefore, lead to defective fibrinolysis and potentially an increased risk of thrombosis. There is, great debate about the significance of hypofibrinolysis as a risk factor for thrombosis.
Case 3

- A 10-day-old baby, previously well, breast fed and born at home is found by his parents unconscious and bleeding from mouth and gums. The only history of note is that the mother had had a major post-partum haemorrhage and had required emergency admission to hospital.

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>102s</td>
<td>11-14s</td>
</tr>
<tr>
<td>aPTT</td>
<td>&gt;120s</td>
<td>23-35s</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>1,9g/l</td>
<td>1,5-4g/l</td>
</tr>
<tr>
<td>Trombin time</td>
<td>13s</td>
<td>10-13s</td>
</tr>
</tbody>
</table>
• Acquired or inherited?
  – the absence of any birth complications, such as umbilical stump
    haemorrhage, an acquired disorder is more likely.

• What could be the problem?
  – This is Vitamin K deficiency. In the 'drama' of the mothers sudden
    admission to hospital vitamin K was not administered to the child and
    it was then forgotten.

• What could confirm that it is vitamin K deficiency and not liver
  insufficiency?
  – Factor V assay would be useful as it is synthesised by the liver but not
    Vitamin K-dependent.
Take home messages

• Bleeding patterns differ in primary and secondary hemostasis defects
• Threshold for prophylactic platelet transfusion
• Role of vWF
• vWD is a frequent mild bleeding disorder
• Importance of factor supplementation, prophylaxis and home treatment in hemophilia
THANK YOU!
Inhibitors

AT: Antithrombin
APC: Activated Protein C
PS: Protein S
TFPI: Tissue Factor Pathway Inhibitor
TF: Tissue Factor

Factors:
- XIIa
- Xa
- Ila
- Va
- VIIIa
- TF-VIIa
- Xa

Inhibitors:
- TFPI
- PS APC

Diagram: Inhibitor (AT) interacts with various factors (XIIa, Xa, Ila, Va, VIIIa, TF-VIIa, Xa) and inhibitors (TFPI, PS APC).
The levels of vitamin K dependent factors are physiologically low at birth. Factors that contribute to this deficiency include:

- Low vitamin K stores at birth
- Poor placental transfer of vitamin K
- Low levels of vitamin K in breast milk [but not in cows milk]
- Sterility of the fetal gut

FINE PRINT

Other possibilities include:
1. A deficiency of factors V, X, or II.
2. Combined factor V + VIII deficiency. However, the PT and APTT are not as prolonged as this results shown above as the levels of FV and FVIII are not completely absent.
3. An inherited deficiency of one of the enzymes involved in the gamma carboxylation of the vitamin K dependent clotting factors. These deficiencies prevent formation of active forms of the vitamin K dependent factors (a similar effect to warfarin) and present very early in life, usually with intracerebral haemorrhage. This is rare but frequent in countries where consanguineous marriages are common.
Fibrinolysis

Fibrinogen

Fibrin Monomer + fibrinopeptides

Thrombin

Soluble fibrin Polymer

XIIIa

Fibrin clot

D-Dimer

Plasmin

(From plasminogen)

Fibrinogen Degradation Products

Fibrin Degradation Products
<table>
<thead>
<tr>
<th>Condition</th>
<th>prothrombin time</th>
<th>aPTI</th>
<th>Bleeding time</th>
<th>Platelet count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K deficiency or warfarin</td>
<td>Prolonged</td>
<td>Normal or mildly Prolonged</td>
<td>unaffected</td>
<td>unaffected</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
<td>Prolonged</td>
<td>Prolonged</td>
<td>Prolonged</td>
<td>decreased</td>
</tr>
<tr>
<td>Von Willebrand disease</td>
<td>unaffected</td>
<td>Prolonged or unaffected</td>
<td>Prolonged</td>
<td>Unaffected (or decreased)</td>
</tr>
<tr>
<td>hemophilia</td>
<td>unaffected</td>
<td>Prolonged</td>
<td>unaffected</td>
<td>unaffected</td>
</tr>
<tr>
<td>aspirin</td>
<td>unaffected</td>
<td>unaffected</td>
<td>Prolonged</td>
<td>unaffected</td>
</tr>
<tr>
<td>thrombocytopenia</td>
<td>unaffected</td>
<td>unaffected</td>
<td>Prolonged</td>
<td>decreased</td>
</tr>
</tbody>
</table>
# Rare factor deficiencies

<table>
<thead>
<tr>
<th>Factor</th>
<th>Symptoms</th>
<th>How much factor is needed</th>
<th>half-time</th>
</tr>
</thead>
<tbody>
<tr>
<td>VII</td>
<td>Mucosal bleeding, muscle, joint bleeding</td>
<td>15-20 %</td>
<td>4-6 hours</td>
</tr>
<tr>
<td>V</td>
<td>Mucosal bleeding</td>
<td>15-20 %</td>
<td>36 hours</td>
</tr>
<tr>
<td>X</td>
<td>Umbilical cord, muscle, joint</td>
<td>15-20%</td>
<td>40-60 hours</td>
</tr>
<tr>
<td>XI</td>
<td>Posttraumatic bleeding</td>
<td>15-20%</td>
<td>70 hours</td>
</tr>
<tr>
<td>XIII</td>
<td>Umbilical cord, intracranial, joint, habitual abortus</td>
<td>2-5%</td>
<td>11-14 days</td>
</tr>
<tr>
<td>I</td>
<td>Umbilical cord, muscle, joint, habitual abortus</td>
<td>0,5g/l</td>
<td>2-4 days</td>
</tr>
<tr>
<td>II</td>
<td>Umbilical cord, muscle, joint</td>
<td>20-30%</td>
<td>3-4 days</td>
</tr>
</tbody>
</table>