Hemorrhagic Diatheses (Bleeding Disorders)

Hemorrhagic diatheses

= higher tendency to bleeding

= pathological states manifested with spontaneous bleeding or more intensive bleeding during injuries or surgery

Hemorrhage

- external, internal (tissues, body cavities)
- arterial, venous, capillary
- massive (acute), chronic

Consequences

→ loss of circulating fluid volume → hypovolemia → shock

→ loss of iron → sideropenic anemia

→ organ compression, inflammation... (internal bleeding)

- intracranial bleeding → brain tissue destruction, intracranial hypertension, obstruction of cerebrospinal fluid spaces (hydrocephalus)
- heart tamponade → diastolic dysfunction
- hemoperitoneum → hematoma organization → adhesions
- hemothorax → restrictive ventilation disorder, adhesions
- hemarthros → restriction of joint movements

Source of bleeding

- Injury of the vessel by external stimuli (sharp, blunt)
- Vessel wall rupture due to high blood pressure

+ weaker vessel wall + disorders of hemostatic mechanisms

Source of internal bleeding, bleeding into cavities

- penerating injuries
- blunt injuries (e.g. fall from height)
- GIT beeding: esophageal varices, gastric ulcers, tumors
- anerysm rupture (aortic aneurysm!)

Hemostatic mechanisms

Primary

- Vessel response
- Thrombocytes (adhesion, aggregation, degranulation)

Secondary

- Coagulation

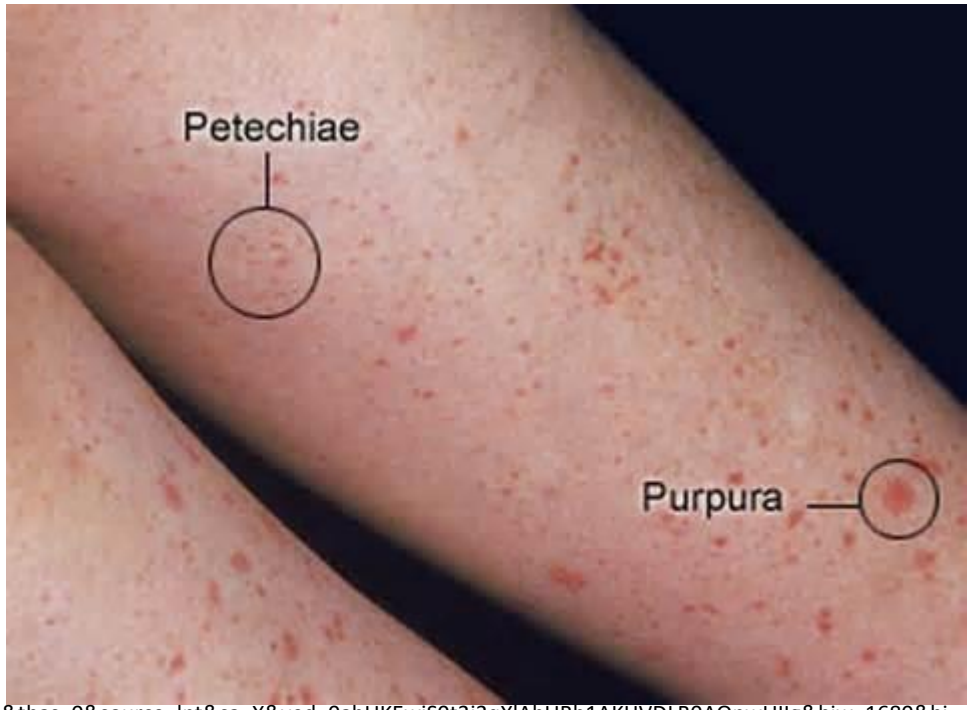
Excessive bleeding can result from:

- Disorders of the vascular wall – increased fragility of vessels
- Disorders of the thrombocytes (thrombocytopenia, thrombocytopathy)
- Disorders of the coagulation factors

Disorders of the vascular wall

- They induce small hemorrhages (petechiae, purpura – purple colored spots) in the skin or mucous membranes.
- More significant hemorrhages can occur into joints, muscles, nosebleeds, gastrointestinal bleeding, hematuria…

hereditary x acquired



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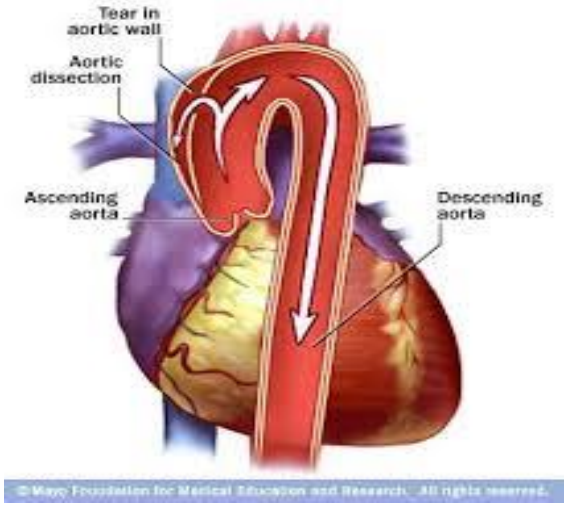
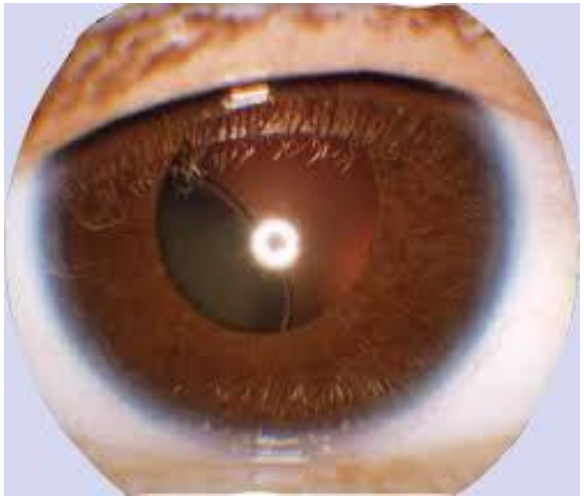
Congenital disorders of vascular wall
Marfan syndrome

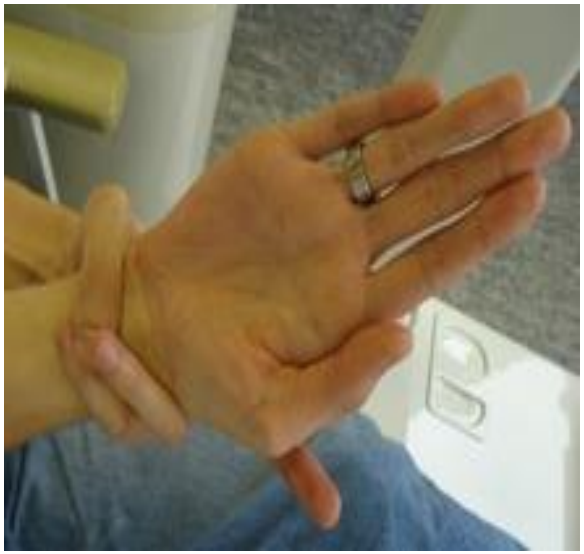
- incidence 5/10 000
- genetic disorder of the connective tissue (AD)
- mutation in FBN1 gene encodes a connective protein fibrillin 1 (required for synthesis of elastic fibers)
- tall people, long limbs, long thin fingers (arachnodactyly)
- complications: defects of the heart valves and aorta, dural ectasia, ectopia lentis – subluxation of ophthalmic lens, spontaneous pneumothorax,

  Aortic dissection!

Congenital disorders of vascular wall
Marfan syndrome







https://en.wikipedia.org/wiki/Marfan_syndrome

Congenital disorders of vascular wall

Hereditary hemorrhagic telangiectasia - Osler–Weber–Rendu disease:

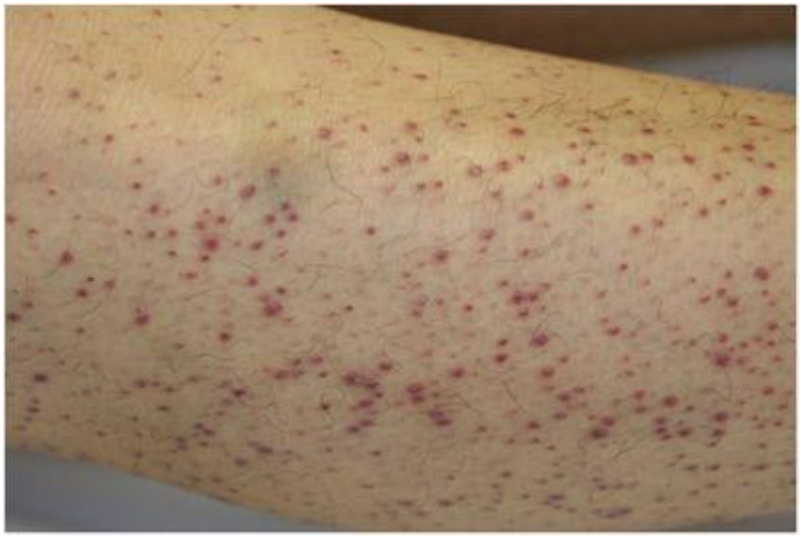
- AD heredity
- Characterized by dilated, tortuous blood vessels, arteriovenous malformations
- Lips, buccal mucous membrane, GIT bleeding, hematuria
- A-V shunts in the lungs → hypoxemia

Ehlers-Danlos syndrome

- a group of disorders affecting connective tissues (impaired collagen formation)
- purpura, joint and skin hyperextensibility

Acquired disorders of vascular wall
Avitaminosis C - scurvy (scorbut)

- chronic vitamin C deficiency (insufficient nutrition)
- impaired synthesis of hydroxyproline (part of collagen) in humans
- bleeding from the mucous membranes (bleeding gums)



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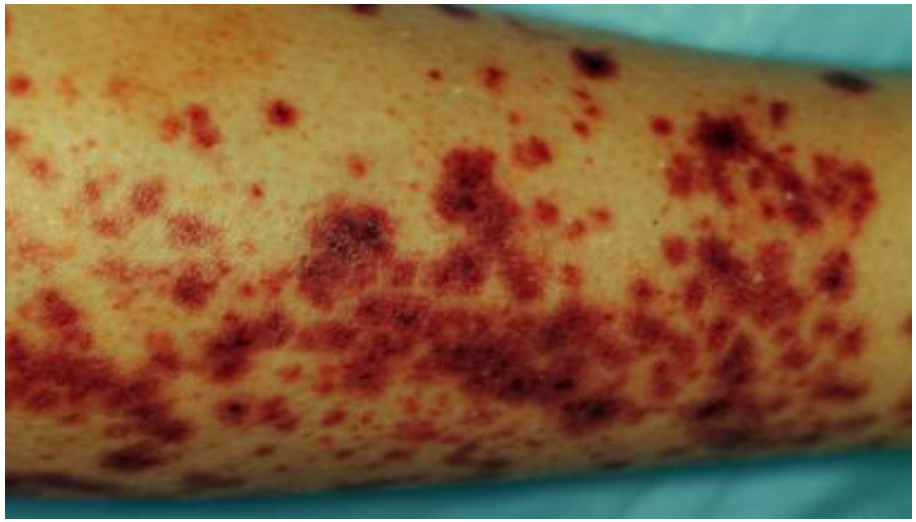
Acquired disorders of vascular wall
Henoch-Schönlein purpura

- anaphylactoid purpura
- systemic autoimmune vasculitis
- deposition of immune complexes containing the antibody IgA in the skin and kidney (it causes increased vascular wall permeability)
- occurs mainly in young children and teens (often follows after infection with beta hemolytic streptococcus)



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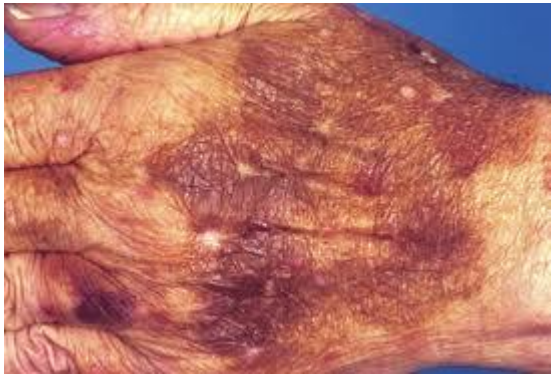
Acquired disorders of vascular wall

Senile purpura: the vascular supporting tissues weaken from age, occurs mostly in the dorsal hands and the extensor surface of forearms



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Steroid purpura: when the vascular supporting tissues are weakened by prolonged topical or oral use of glucocorticoids

Many **infections** (measles, scarlet fever, bacterial exotoxins) induce petechial and purpuric hemorrhages

Rumpel-Leede test

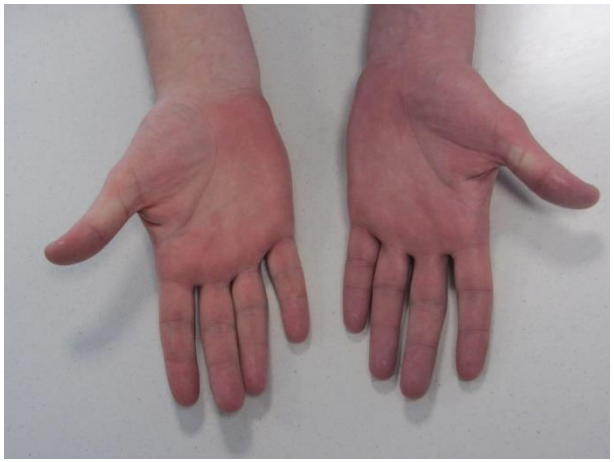
- to detect vasculopathies

1) Measure systolic and diastolic blood pressure
2) Calculate MAP

$$MAP = 1/3\ SAT + 2/3\ DAP$$

3) Maintain tonometer cuff on the arm inflated to the level of MAP for 10 min
4) Release the cuff
5) Examine petechia presence on the forearm

- Semi-quantitative evaluation (0, +, ++, +++)



Thrombocyte-related hemorrhagic diatheses

- thrombocytopenia = low number of thrombocytes
- thrombocytopathy = wrong function of thrombocytes (adhesion, aggregation, degranulation)
- combination of both

Reduced platelet number - thrombocytopenia

- normal range from 150 000 up to 300 000/µl
- a count bellow 100 000/µl: clinically significant thrombocytopenia
- a count below 20 000/µl – risk of spontaneous bleeding – in the skin and mucous membranes, gastrointestinal and genitourinary tract, CNS…
- a count below 5 000/µl – extreme risk of spontaneous bleeding!

Causes of thrombocytopenia

- decreased production of platelets
- decreased platelet survival (platelet loss)

Decreased production of platelets

- generalized diseases of bone marrow – aplastic anemia, leukemias, disseminated cancer, myelofibrosis…
- impairment of platelet production – cytotoxic substances (including medicaments), vitamin B12 or folic acid deficiencies, irradiation (including radiotherapy), alcohol - cirrhosis (low thrombopoietin level)

Decreased platelet survival

Immunologic etiology: ITP (Immune thrombocytopenic purpura) – acute x chronic

- platelet destruction results from the formation of antiplatelet autoantibodies of the IgG class (cross-reaction of anti-virus and anti-platelet antibodies-after a viral infection)
- opsonized platelets are rendered susceptible to phagocytosis
- other immune mediated disorders: SLE (systemic lupus erythematosus)…

Non-immune destruction of platelets – mechanical injury (prosthetic heart valves…)

Decreased platelet survival
Thrombotic thrombocytopenic purpura (TTP)

- the underlying mechanism typically involves antibodies inhibiting the enzyme *von Willebrand factor-cleaving protease* this results in decreased break down of von Willebrand factor (vWF)
- **spontaneous adhesion and aggregation of platelets**, thrombocytopenia, hemolytic anemia (microangiopathic hemolytic anemia)
- platelets are used up in the formation of thrombi, this then leads to a decrease in the number of overall circulating platelets

Qualitative defects of platelet function - **Thrombocytopathy**

Congenital

- AR disorder of the platelet membrane glycoprotein complex Ib-IX, impaired platelet **adhesion**! (Bernard-Soulier syndrome)
- AR defective platelet **aggregation** – glycoprotein IIb-IIIa (Glanzmann´s thrombasthenia)
- Chediak-Higashi syndrome: AR impaired **storage and degranulation** function of platelets

Acquired

- Aspirin (acetylsalicylic acid) or other nonsteroidal anti-inflammatory drugs (NSAID)
- Irreversible inhibitors of the enzyme cyclooxygenase (COX), which is required for the synthesis of thromboxane A2 and prostaglandins – impaired platelet **aggregation** (but useful as prophylaxis of thrombosis)!

Von Willebrand's disease

- quantitative or qualitative defect of vW factor (carrier protein for factor VIII, acts as a bridge between platelets and the endothelium): impaired adhesion of platelets, instability of factor VIII in plasma
- hereditary (AD) x acquired (synthesis of antibodies against vW factor)

Coagulopathies

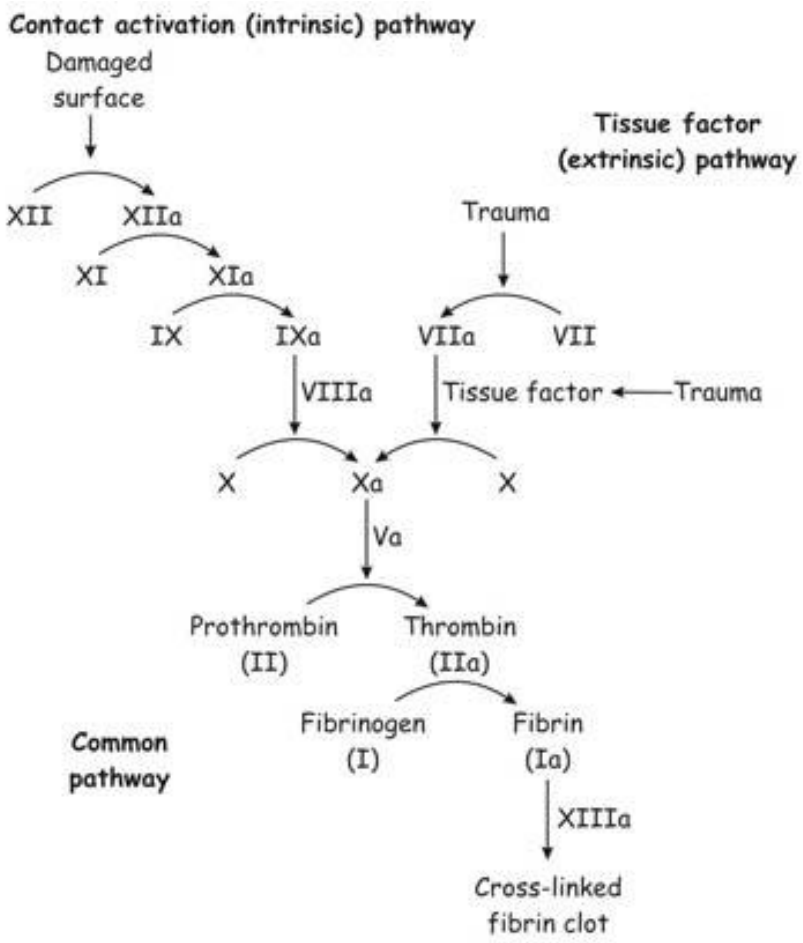
The bleeding is manifested by large post-traumatic hematomas, prolonged bleeding after a laceration or any form of surgical procedure, bleeding in the gastrointestinal and urogenital tract, epistaxis, large hematomas in muscles, retroperitoneum, brain (prolonged and repeated bleeding).

Hemarthrosis after relatively trivial stress into a knee joint!

Petechiae are characteristically **absent!**

Hereditary x acquired disorders

Blood coagulation



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Plasma Clotting Factors

No.	Factor name	Function	Pathway
I	Fibrinogen	Converted to fibrin	Common
II	Prothrombin	Converted to thrombin (enzyme)	Common
III	Tissue factor (thromboplastin)	Cofactor	Extrinsic
IV	Ca^{2+}	Cofactor	Intrinsic, extrinsic, common
V	Proaccelerin	Cofactor	Common
VI	= activated f. V		
VII	Proconvertin	Enzyme	Extrinsic
VIII	Antihemophilic factor	Cofactor	Intrinsic
IX	Christmas factor	Enzyme	Intrinsic
X	Stuart-Prower factor	Enzyme	Common
XI	Plasma thromboplastin antecedent	Enzyme	Intrinsic
XII	Hageman factor	Enzyme	Intrinsic
XIII	Fibrin stabilizing factor	Enzyme	Common

Hereditary disorders of clotting factors
Hemophilia A – factor VIII deficiency

- X-linked recessive trait, but 30% of patients have no family history – new mutations!
- incidence of about 1 patient per 10 000 inhabitants
- clinical severity correlates with the level of factor VIII activity (normal 0.1mg/l)
- combination with Leiden (factor V) mutation – only mild manifestation!
- less than 1% of normal activity of factor VIII – severe disease
- the most common type of symptoms is bleeding into joints
- treatment: infusion of recombinant factor VIII, fresh frozen plasma

Hereditary disorders of clotting factors

Hemophilia B: (factor IX deficiency)

- X-linked recessive trait or new mutations
- incidence 1:70 000
- variable clinical severity
- recombinant factor IX is used for treatment

Hemophilia C: (factor XI deficiency)

- AR heredity
- commonly seen in Ashkenazi Jews
- only mild bleeding tendency

Hereditary disorders of clotting factors

Congenital afibrinogenemia

Congenital dysfibrinogenemia

- nonsense or missense mutation of genes that encode the fibrinogen protein

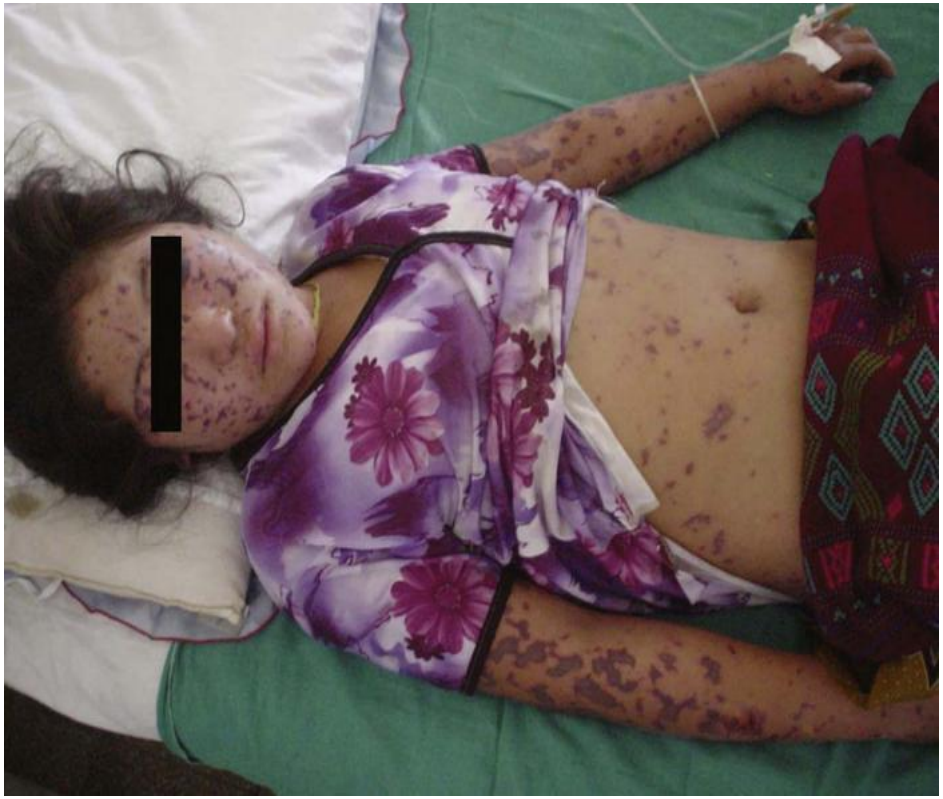
Acquired disorders of coagulation
DIC – disseminated intravascular coagulation

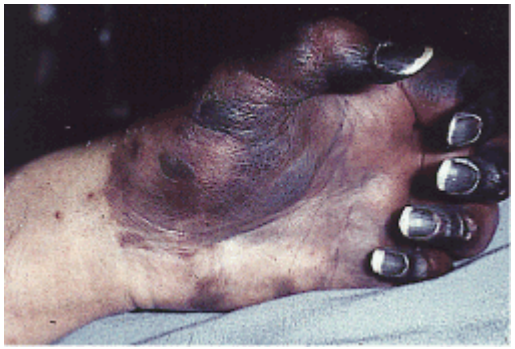
- severe hemorrhagic disorder – secondary complication of variety of diseases: neoplasms (penetration of tumor cells into the circulation), massive tissue injury, infections (sepsis), obstetric complications (abruptio placentae, septic abortion, amniotic fluid embolism)…

- **release of tissue factor (III) into the circulation (alien cells) or pathological expression of factor III on the surface of the endothelium**

- activation of the coagulation cascade that leads to the formation of microthrombi in the microcirculation of the body
- consequences: consumption of platelets, fibrin, coagulation factors, and secondarily, activation of fibrinolytic mechanisms aggravates the hemorrhagic diathesis…..fatal hemostatic failure

Acquired disorders of coagulation
DIC – meningococcal sepsis (mortality 25%)





https://www.priznaky-projevy.cz/interna/hematologie/137-dic-diseminovana-intravaskularni-koagulace-priznaky-projevy-symptomy

Acquired disorders of coagulation
Vitamin K deficiency

Vitamin K:

- an essential, **lipid-soluble** vitamin that plays a vital role in the production of coagulation proteins (factors II, VII, IX, X)
- is found in green, leafy vegetables and in oils, such as soybean, canola, and olive oils
- is also synthesized by **colonic bacteria**
- deficiency: long-term antibiotic therapy, obstructive jaundice, liver failure from various reasons

Acquired disorders of coagulation
Pharmacologically induced coagulopathies

Warfarin

- Indirect p.o. anticoagulant
- Blocking vit. K
- Vit. K has an antagonistic effect (with a delay!) → Therapy effect depends on vit. K intake
- For fast restoration of clotting in a warfarin-overdosed patient substitution of K-dependent clotting factors (e.g. fresh plasma administration) is necessary.
- Therapy control: Quick test

Acquired disorders of coagulation
Pharmacologically induced coagulopathies

Heparin

- → antithrombin activation (1000x) → inactivation of thrombin and Xa
- Heparin - i.v.
- Low-molecular heparins - s.c.
- Antidote: protamine sulphate
- Therapy control: aPTT (activated partial thromboplastin time)

Gatrans

- direct thrombin inhibitor

Xabans

- direct Xa inhibitor

Thrombophilia (hypercoagulability)

- increases the risk of thrombosis
- the most common symptoms: recurrent deep vein thrombosis, pulmonary embolism
- congenital x acquired disorders

Congenital thrombophilias

Impaired inhibition of clotting factors:

Factor V Leiden: variant (mutated form) of human factor V, protein C is not able to bind to factor V and cleave it, homozygous form increases the risk of thrombosis around eighty times the normal risk!

Protein C deficiency (inactivates f. V and VIII and tPA inhibitor)

Protein S deficiency (protein C cofactor)

Antithrombin deficiency

Impaired fibrinolysis:

Deficiency of plasminogen

Deficiency of tPA (tissue plasminogen activator)

→ impaired clot dissolving

Acquired thrombophilias

usually start in adulthood

Conditions affecting the endothelial surface: atherosclerotic vascular changes, injury, inflammation (endocarditis, phlebitis)

Slowing of blood flow: heart failure, immobilization, turbulent blood flow (atrial fibrillation)

Pathological presence of tissue factor (III) in circulation: advanced cancer, injury, sepsis…

Administration of estrogens: estrogens reduce the level of antithrombin

THE END