**DRUGS AFFECTING BLOOD**

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**Hemostasis**

The process of stopping bleeding in damaged or ruptured blood vessel

- To prevent blood loss
- To stop bleeding
- To maintain blood in a fluid state (prevents thrombosis)

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**Vascular constriction**

- Pain
- Moderate to severe reduction in blood flow
- Independent of blood coagulation
- Short period (5 – 20 min)

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**Platelet adhesion**

- Inhibitors of platelets adhesion in intact vessels:
  - Prostacyclin
  - Nitric oxide
- Injury to the intima
- Exposure to subendothelial extracellular matrix proteins (collagen, fibronectin, von Willebrand Factor)
  - Rapid localisation of platelets to the site of injury
  - Formation of a platelet plug

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**Platelets activation**

- Agonists – vWF, thrombin, ADP, thromboxane A₂ (TXA₂), serotonin, epinephrine, vasopressin, fibrinogen, immune complexes, plasmin, PAF
- Changes in the platelet shape
- Degranulation of cytoplasmic vesicles
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<td>Sites of endothelial damage</td>
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<td>Sites of endothelial damage</td>
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<td>Sites of endothelial damage</td>
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<tr>
<td>seconds</td>
<td>Sites of endothelial damage</td>
</tr>
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</table>

| Thrombosis – pathological process in which a platelet     | Arterial occlusion                                        |
| aggregate and/or a fibrin clot occludes the blood vessel. | Myocardial infarction                                    |
|                                                           | Stroke                                                   |
|                                                           | Peripheral ischemia                                      |
|                                                           | Venous occlusion                                         |
|                                                           | Deep venous thrombosis                                   |
|                                                           | Pulmonary embolism                                        |
|                                                           | Sites of endothelial damage                              |
|                                                           | Stasis                                                   |
|                                                           | Increased systemic coagulability                         |
|                                                           | Damaged heart valves                                     |
|                                                           | DIC                                                      |
**Drug affecting blood**

- Platelet inhibitors
- Anticoagulants
- Thrombolytic agents

**Platelet inhibitors**

- Aspirin
- Clopidogrel
- Ticlopidin
- Glycoprotein IIb/IIIa receptor antagonists

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**Aspirin**

- Acetic acid ester of salicylic acid; acetylsalicylic acid
- Antiplatelet agent
- Prevention and treatment of arterial thrombotic disorders
  - Angina pectoris
  - Myocardial infarction
  - Ischemic stroke

**Aspirin - pharmacokinetics**

- Rapidly absorbed from GI tract
- Partially hydrolyzed to salicylate on first pass through the liver
- Widely distributed into body tissues

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**Aspirin - unwanted effects**

- Gastrointestinal irritation
- Bleeding time is prolonged
- Increased incidence of hemorrhagic stroke
- Increased incidence of gastrointestinal bleeding (ulcer)
- „Aspirin asthma“

**Ticlopidine**

- Inhibits ADP-dependent aggregation of the platelet
- Decreases the incidence of thrombotic stroke
  - **Clinical uses:**
    - For patients who cannot tolerate Aspirin
  - **Unwanted effects:**
    - Nausea, vomiting and diarrhea
    - Prolonged bleedings
    - Neutropenia, agranulocytosis
**Clopidogrel**
- Analog of ticlopidine
- Inhibits ADP-induced aggregation
- More effective than Aspirin
- Recommended for patients before PTCA
- The main unwanted effect is bleeding
- It can inhibit cytochrome P-450 so it may interfere with metabolism of other drugs

**Antagonists of GP IIb/IIIa receptors**
- ABCIKSIMAB – monoclonal antibody
- TIROFIBAN – oligopeptid
- By binding to GP IIb/IIIa receptor they block the binding of fibrinogen and other factor and aggregation does not occur – they inhibit all pathways of platelet activation

**Antagonists of GP IIb/IIIa receptors**
- **Clinical uses:**
  - in high-risk patients undergoing coronary angioplasty to reduce the risk of restenosis
- **Unwanted effects:**
  - potential of bleeding
  - Immunogenicity
  - They are used intravenously for single administration
  - May be used in combination with heparin or aspirin

**Anticoagulants**
- Heparin
- Enoxaparin
- Vitamin K antagonists
  - Warfarin
  - Acenocoumarol

**Anticoagulants – clinical use**
- Prevention of:
  - Deep vein thrombosis
  - Extension of established deep vein thrombosis or recurrence of pulmonary embolus
  - Thrombosis and embolisation in patients with atrial fibrillation
  - Thrombosis on prosthetic heart valves
  - Cardiac events in patients with unstable coronary syndromes
  - Clotting in extracorporeal circulations (haemodialysis or bypass surgery)

**Heparin**
- Family of mucopolisacharides
- Together with histamine present in the granules of mast cells
- Inhibits coagulation by activating antithrombin III, which inhibits thrombin (IIa), factor Xa and other serine proteases by binding to the active site
- Is given intravenously or subcutaneously
- The activated partial thromboplastin time (APTT) must be measured (targeted range 1.5-2.5 times control)
Heparin – clinical use

- Preventing venous thrombosis
- Treating deep venous thromboembolism and pulmonary embolism
- The early treatment of patients with unstable angina and acute myocardial infarction
- Preventing clotting in catheters used to cannulate blood vessels

Heparin – adverse effects

- Hemorrhage
- Hypersensitivity reactions: chills, fever, urticaria and even anaphylactic shock
- Thrombocytopenia (after 8-10 days of treatment) with or without thrombosis
- Bone loss
- Heparin-induced bleeding \( \Leftrightarrow \) protamine sulfate
  100 units heparin / 1 mg protamine sulfate

Enoxaparin

- One of low-molecular-weight heparins (LMWHs); fractionated heparin
- Increases the action of antithrombin III on factor Xa
- Does not act on thrombin
- Has a longer elimination half-time than heparin
- Does not prolong the APTT

Low-molecular-weight heparins

- Ardeparin
- Dalteparin
- Nadroparin
- Parnaparin
- Certoparin
- Tinzaparin
- Reviparin

Lepirudin (hirudin)

- Recombinant protein, derived from yeast cells
- Potent direct inhibitor of thrombin
- Clinical use – thrombosis complications related to heparin-induced thrombocytopenia
- Adverse effects – bleeding, abnormal liver function, allergic skin reactions

Prothrombin complex

- II (prothrombin)
- VII
- IX
- X
**Warfarin**

- Warfarin has structural similarity to vitamin K
- Inhibits activation of factors II, VII, IX, X, which are depend on present of vitamin K
- Pharmacological effect is delayed, it can occur about 48 hours after first administration
- The effect must be monitored by measuring INR (target range 2-3)
- Dose are given individualised according to INR.

**Warfarin – clinical use**

- Prevention and treatment of venous thromboembolism and pulmonary embolism
- Prevention of thrombotic and embolic strokes
- Prevention of recurrence of infarction
- Patients with mechanical prosthetic valves
- Atrial fibrillation

**Warfarin – adverse effects**

- Hemorrhage and bleeding
- Skin necrosis
- Cause abortion
- It is teratogenic agent

**Thrombolytic agents**

- Streptokinase
- Alteplase
- Urokinase

**TA – clinical use**

- Acute myocardial infarction within 12 hours of onset
  THE EARLIER THE BETTER!
- Acute thrombotic stroke within 3 hours of onset (in selected patients)
- Acute arterial thromboembolism
- Clearing arterial shunts and cannulae

**Streptokinase**

- Protein extracted from culture of streptococci
- Activates free plasminogen to convert to plasmin, which in turn cleaves fibrin, thus lysing thrombi
- **Adverse effects:**
  - Bleeding disorders
  - Hypersensitivity – rashes, fever, anaphylactic shock
  - Drug does not act in patients who have circulating antibodies against streptokinase (in case streptococcal infection) – they may neutralize its fibrinolytic effect
Alteplase

- Known as tissue-type plasminogen activator (tPA)
- Is a serine protease from cultured human melanoma cells
- Activates only plasminogen bound to fibrin in a thrombus or a hemostatic plug ("fibrin selective")
- Adverse effects – BLEEDING complication (gastrointestinal and cerebral hemorrhages)

Urokinase

- Produced in kidney
- Directly converts plasminogen to plasmin by cleaving the arginine-valine bond in plasminogen
- Directly degrades fibrin and fibrinogen

TA – contraindications

- Acute pericarditis
- Active internal bleeding
- Recent cerebrovascular accident
- Metastatic cancer

Bleeding disorders

- Vascular defects include acquired or hereditary structural abnormalities of blood vessel wall
- Platelet defects include acquired or hereditary abnormalities in platelet quantity (thrombocytopenia) or platelet quality (thrombocytopathy)
- Defects of coagulant factors (hemophilia, von Willebrand disease)

Methods of controlling bleeding

<table>
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<tr>
<th>Desired result</th>
<th>Physiologic methods</th>
<th>Physical methods</th>
<th>Chemical agents</th>
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<tbody>
<tr>
<td>Hemostasis</td>
<td>Vasoconstriction, platelet plug, clot retraction</td>
<td>Pressure, electrocautery, cooling, sutures</td>
<td>Epinephrine, astringents, styptics</td>
</tr>
<tr>
<td>Clotting</td>
<td>Procoagulants, thrombin, platelets, other clotting factors</td>
<td>Physical maliness, gelatin, cellulose, collagen</td>
<td>Topical thrombin, fibrin sealant, antifibrinolytics</td>
</tr>
</tbody>
</table>

Genetically based disorders of coagulation

- Hemophilia A – factor VIII
- Hemophilia B – factor XI
- Von Willebrand’s disease
### Coagulation factors concentrates
- Factor VIII concentrates – hemophilia A
- Factor IX concentrates – hemophilia B

### Desmopressin
- Synthetic analog of vasopressin
- Causes the release of von Willebrand factor and factor VIII from body storage sites
- Patients with mild factor VIII deficiency and von Willebrand disease
- Intranasal spray, intravenous or subcutaneous injection

### Vitamin K
- Essential factor for the liver synthesis of prothrombin, factors VII, IX, X, protein C and protein S
- **Clinical uses:**
  - Reversing bleeding caused by vitamin K antagonists
  - Patients with vitamin K deficiency
  - Preventing hypoprothrombinemia in the newborn

### ε-aminocaproic acid (EACA)
- Inhibits the fibrinolytic system
- Oral and parenteral formulations
- **Clinical use** – treatment of many bleeding conditions (urinary tract)
- **Adverse effects** – intravascular thrombosis, hypotension, myopathy, diarrhea, nasal stuffiness

### Aprotinin
- Protein purified from bovine lung
- Inhibitor of several serine proteases including tissue and plasma kallikrein – decrease in the formation of activated coagulation factor XII
- **Clinical use** – reduction of blood loss during cardiac surgery
- **Adverse effect** – hypersensitivity reactions

### Topical absorbable hemostatics
- Thrombin
- Micronized collagen
- Absorbable gelatin
- Oxidized cellulose
Soft tissue bleeding
- Pressure with sterile cotton gauze
- Hemostats
- Ligation
- Electrocautery
- Microfibrillar collagen or collagen sheets

Bleeding from bony structures
- Pressure with sterile cotton gauze
- Collagen plug or gelatin sponge

Astringents and Styptics
- Hemostasis while retracting gingival tissue
- Salts of zinc, silver, iron and aluminium
- Tannic acid
  - Denaturation of tissue and blood protein
  - Agglutination
  - Plug

Vasoconstrictors
- Epinephrine
  - Solutions
  - Dry cotton pellets impregnated with epinephrine
- Tetrahydrozoline
- Oxymetazoline

Patients receiving anticoagulants
- Bleeding after surgery
- Thromboembolic events
- Drug interactions

Any intended oral surgical therapy in anticoagulated patients required preliminary planning and consultation with the patients’ physician

INR

<table>
<thead>
<tr>
<th>INR</th>
<th>Extent of surgery?</th>
<th>No surgical treatment until INR is reduced</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4</td>
<td>Minimal bleeding expected</td>
<td>Consider reducing INR; use local measures</td>
</tr>
<tr>
<td>&gt;4</td>
<td>Moderate bleeding expected</td>
<td>Modify anticoagulation to achieve an INR &lt; 3; use local measures</td>
</tr>
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</table>
**Anemia**

- Reduction in the red blood cell mass
- Hematocrit value less than
  - 37% - women
  - 40% - men
- Symptoms – pale skin, fatigue, shortness of breath, cold extremities, lightheadedness, headaches, weakness, inflammation of the tongue, soreness of the tongue, brittle nails, cravings for non-nutritional substances such as ice, dirt, or pure starches, poor appetite especially in children or babies

**Consequences of chronic anemia**

- Reduced function and quality of life
- Decreased survival (<65 years)
- Increased risk of heart failure
- Increased risk of coronary death
- Changes in neurological function

**Causes of anemia**

- **Hypoproliferative**
  - Microcytic
    - Iron deficiency
    - Chronic disease
    - Sideroblastic anemia
  - Normocytic
    - Chronic disease
    - Endocrine anemia
    - Bone marrow failure
  - Macrocytic
    - Vitamin B12 deficiency
    - Folic acid deficiency
    - Myelodysplastic syndrome

- **Hyperproliferative**
  - Hemolytic
    - Hemoglobinopathies
    - Autoimmune
    - Membrane disorder
    - Drug-induced
    - Metabolic abnormalities
    - Infections

**Iron-deficiency anemia**

- Iron deficiency
  - Rapid growth phase
  - Chronic bleeding
  - Pregnancy
  - Low iron diet
  - Inability to absorb iron
  - Iron is needed to form the complex molecule, heme, which is the oxygen-carrying component of hemoglobin

**Life stages prone to iron deficiency**

- Children under 2 years
- Adolescence – especially girls
- Pregnancy
- Elderly

**Physiologic loss of iron**

- 1 mg/day – men and nonmenstruating women
- 2 – 3 mg/day – menstruating women
- 500 – 1000 mg – each pregnancy
**Iron-deficiency anemia treatment**
- Correction of underlying causes of iron deficiency
- Iron replacement therapy – ferrous sulfate
  - Oral administration
  - 150-200 mg of elemental iron per day (3-4 doses)
  - Continue for 6 months after normalization of Hb level
- Parenteral preparations – intramuscular and intravenous

**Macrocytic anemias**
- Megaloblastic anemia – biochemical defect in DNA synthesis
- Nonmegaloblastic anemia – pathological alteration in membrane lipids of RBC

**Vitamin B₁₂ deficiency**
- Dietary deficiency
- Pernicious anemia
- Malabsorption syndrome
- Gastrectomy
- Inflammatory bowel disease
- Small bowel resection

**Vitamin B₁₂ deficiency**
- Parenteral therapy – initial dose 0.1-1 mg/day of vit.B₁₂ i.m. for 1-2 weeks; maintenance dose – 1 mg monthly
- Oral therapy, intranasal gel

**Purposes of folic acid**
- Folic acid is necessary for the production and maintenance of new cells
- Metabolism of serine, glycine, methionine, and histidine
- Purine and pyrimidine synthesis

**Folic Acid and Pregnancy**
- Folic acid is very important for all women who may become pregnant
- Protection against a number of congenital malformations including neural tube defects
- Neural tube defects result in malformations of the spine (spina bifida), skull, and brain (anencephaly)
Folic Acid Deficiency

- Megaloblastic anemia
- In infants and children, folic acid deficiency can slow growth rate
- Diarrhea, loss of appetite, weight loss, weakness, sore tongue, headaches, heart palpitations, irritability, and behavioural disorders

Folic acid deficiency

- Pregnancy, alcohol abuse, prolonged biliary drainage, antifolates
- Oral folate 1-5 mg/day
- Vitamin B12 deficiency may cause concomittant folate deficiency!!!

Erthropoietin

- Stimulates red blood cells production
- Indications
  - Anemia of chronic renal failure
  - Anemia secondary to chemotherapy
  - Anemia secondary to cancer, chronic inflammatory diseases, AIDS and diabetes
- Epoietin, darbepoietin (IV or S.C.)