ANTITHROMBOTIC DRUGS

1- **Antiplatelets**: for prophylaxis of thromboembolic disease.
2- **Anticoagulants**: for prevention of thromboembolic disease.
3- **Fibrinolytics**: for rapid dissolution of thromboemboli

### (1) Anticoagulants

**Classification:**

1) **In vitro only anticoagulants:**
   - Substances which remove ionic calcium
   - Used in laboratory blood samples
   - They include:
     a- **Calcium precipitants**: e.g.: Na or K oxalate
     b- **Diminished ionized calcium**: e.g.: Na citrate (in blood samples and banks) and EDTA.

2) **In vivo anticoagulants:***
   1- **Direct acting (Thrombin inhibitors):**
      a- Indirect thrombin inhibitors:
         - Antithrombin III activator: **Heparins**
         - Unfractionated Heparin (UFH)
         - Low molecular weight Heparin (LMWH)
         - Selective factor Xa inhibitor: **Fondaparinux**
      b- Direct thrombin inhibitors:
         - **Hirudin**
         - Recombinant hirudin (Lepirudin – Bivalirudin)
         - Synthetic: (Argatroban – Ximelagatran)

2- **Indirect acting (Vit. K antagonists):**
   a. Coumarins: **Dicoumarol – Warfarin**
   b. Indanedione: **Phenindion (Dindivan) - Diphenadion**

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**N.B:** Oral anticoagulants include: vit. K antagonists & Ximelagatran

**N.B:** **Ancrod**: extract of viper venom that deplete circulating fibrinogen
**Comparison between Heparin and Warfarin**

<table>
<thead>
<tr>
<th></th>
<th>Heparin* (Unfractionated heparin)</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Source</strong></td>
<td>- Naturally found with histamine in mast cells in liver &amp; lung</td>
<td>- Coumarin** is natural</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Warfarin*** is Synthetic</td>
</tr>
<tr>
<td><strong>Chemistry:</strong></td>
<td>- Mucopolysaccharide strongly acidic with strong <em>electronegative charge</em></td>
<td>- Coumarine derivative</td>
</tr>
<tr>
<td><strong>Kinetics:</strong></td>
<td>- Parenterally (I.V.) or (S.C) never I.M (haematoma)</td>
<td>- Given orally, bound to plasma protein</td>
</tr>
<tr>
<td></td>
<td>- Metabolized in liver and tissues (by heparinase enzyme)</td>
<td>- Metabolized in liver</td>
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<td></td>
<td>- Not cross the placenta &amp; Not secreted in milk (Allowed in pregnancy &amp; lactation)</td>
<td>- Cross the placenta &amp; secreted in milk (Not Allowed in pregnancy &amp; lactation)</td>
</tr>
<tr>
<td></td>
<td>- Excreted in urine</td>
<td>- Excreted in urine &amp; milk</td>
</tr>
<tr>
<td><strong>Onset &amp; Duration:</strong></td>
<td>- Immediate after I.V.</td>
<td>- Delayed onset 1-2 days</td>
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<tr>
<td></td>
<td>- Short duration [4 hr after I.V.]</td>
<td>- Long duration [4-7 days]</td>
</tr>
<tr>
<td><strong>Actions:</strong></td>
<td>1) <strong>Anticoagulant</strong> in vivo &amp; vitro Potentiating the action of <em>antithrombin III</em> which neutralizes &amp; inhibit many clotting factors</td>
<td>1) <strong>Anticoagulant</strong> in vivo only</td>
</tr>
<tr>
<td></td>
<td>2) <strong>Lipaemea clearing action</strong> due to activation of lipoprotein lipase enz.</td>
<td>↓ Vit.K reductase enz.</td>
</tr>
<tr>
<td><strong>Dose:</strong></td>
<td>* Initially: 70-100 U / kg</td>
<td>- Initially 10 mg/day 3 doses</td>
</tr>
<tr>
<td></td>
<td>* Maintenance: infusion 15-25 U/kg/h</td>
<td>- Maintenance 4-5 mg / day</td>
</tr>
<tr>
<td><strong>Control of the dose:</strong></td>
<td>(1) <strong>Coagulation time:</strong> Prolonged 2-2.5 times (normally 5-7 min.)</td>
<td>(1) Prothrombin time (PT):</td>
</tr>
<tr>
<td></td>
<td>(2) <strong>Partial thromboplastin time (PTT):</strong> Prolonged 2-2.5 times (normally 30-40 sec.)</td>
<td>- Prolonged to 2-2.5 times (normally 12-15 seconds)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*NB: International Normalized Ratio (INR) is more accurate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>= PT of patient / PT of normal</td>
</tr>
<tr>
<td><strong>Uses</strong></td>
<td>1) <strong>Treatment of thromboembolic disease:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Myocardial infarction</td>
<td></td>
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<tr>
<td></td>
<td>- Pulmonary embolism</td>
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<tr>
<td></td>
<td>- Venous &amp; Cerebral thrombosis</td>
<td></td>
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<tr>
<td></td>
<td>2) **Prophylactic:**of venous thrombosis &amp; Pulmonary embolism [not effective on arterial thrombosis]</td>
<td></td>
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<tr>
<td></td>
<td>3) <strong>Prevent blood clotting</strong> During transfusion (heparin)</td>
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<td></td>
<td>4) <strong>In hyperlipidemia</strong> (heparin)</td>
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</tbody>
</table>

*Heparin: was discovered by a medical student in 1916 in a physiological research to study clotting substances in the body. To his surprise he found that extract from the liver retarded the clotting process, and hence its name “hepa”

**Coumarin: was discovered as an anticoagulant substance formed in spoiled sweet clover silage which caused hemorrhage in cattle

***Warfarin: the name is derived from the patent holder, Wisconsin Alumni Research Foundation & “arin” from coumarin
**Blood**

### Side effects

1. **Hemorrhage**
2. **Hypersensitivity**
3. Hyperkalemia (antagonize aldosterone)
4. Hair loss (transient alopecia)
5. Osteoporosis
6. *Thrombocytopenia & paradoxical thrombosis*

### Antidote

1. **Protamine sulphate I.V.:** 1 mg for 100 U (1ml) heparin (Strongly electropositive charged)
2. Fresh blood transfusion

### Contraindication

1. Allergy to the drug
2. Liver & kidney disease
3. Anticoagulant not desired:
   - Active T.B
   - Subacute bacterial endocarditis
   - Peptic ulcer & ulcerative colitis
4. Bleeding conditions:
   - Bleeding tendency (haemophilia)
   - Head injury
   - Threatened abortion
   - Visceral carcinoma

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**Drug, food & disease interactions of Oral anti-coagulants**

**1) ↑ Anti coagulant effect may be due to:**

1. **Kinetic interaction:**
   a. Displacement from plasma proteins by: Aspirin- Phenylbutazone- Indomethacin- Clofibrate- Sulphonamide- Sulphinpyrazone
   b. HME inhibitor as Cimitidine- Chloramphenicol- Allopurinol

2. **Dynamic interaction:**
   a. ↓ vit K:  ↓ synthesis by broad spectrum antibiotics, e.g.: Tetracycline
   - ↓ absorption by liquid paraffin
   b. ↓ Platelet aggregation & function as
   - Aspirin S.D
   - Cephalosporins (third generation) [Also have anti vit K affect]
   c. Androgen [due to ↑ turnover of clotting factors]

3. **Pathological:** Liver disease, hyperthyroidism

**2) ↓ anti coagulant effect may be due to:**

1. **Kinetic interaction:**
   - ↓ Absorption as cholestyramine
   - ↑ Metabolism by HME inducers as phenobarbitone- rifampicin- griseofulvin

2. **Dynamic interaction:**
   - ↑ Clotting factors by estrogen
   - vit.K (including food rich in vit. K as green, leafy vegetables)

3. **Pathological:** Hypothyroidism & hereditary resistance
N.B.: Choice of anticoagulant:
- Begin therapy with heparin and oral anticoagulant together then after 4-5 days withdraw heparin and maintain on oral anticoagulant for 3 months
- Heparin is used for emergency & during pregnancy

*N.B.: Heparin induced Thrombocytopenia:
- Types:
  - Type I: Mild - Non immunologic induction of platelet aggregation
  - Type II: Severe - Immunological induced platelet aggregation due to formation of immune complexes
- May cause paradoxical thrombosis
- Management: Stop heparin & replace by another anticoagulant as direct thrombin inhibitors

LMW heparins
- Examples: Enoxaparin – Dalteparin – Rivaparin - Danaproid
- Mechanism of action: potentiate the effect of antithrombin III selectively on activated factor X & have less effect on other coagulation factors.
- Differences versus Unfractionated heparin:
  - They have equal efficacy to UFH
  - Increased S.C bioavailability
  - Less frequent dose administration
  - Can be given without laboratory monitoring

Direct thrombin inhibitors
- Uses:
  As alternative to heparin for patients with heparin induced thrombocytopenia

- Differences versus Heparin:
  They produce a more predictable anticoagulant response than UFH because they do not bind to plasma proteins & are not neutralized by platelet factor 4, a heparin-binding protein released from activated platelets.

- Include:
  - Hirudin
  - Recombinant hirudin (Lepirudin – Bivalirudin)
  - Synthetic: (Argatroban – Ximelagatran)

N.B.: Ximelagatran is the only one of this group which is given orally, while others are given IV

N.B.: Drotrecogin Alfa (Xigris); is a recombinant form of protein C that inhibits coagulation by proteolytic inactivation of factors Va & VIIIa. It has also anti-inflammatory effect & used as IV infusion in cases of severe sepsis
2) Anti-Platelet Agents

**Uses:**
1- Prevention & treatment of occlusive cardiovascular disease (eg.: Angina)
2- Maintain vascular grafts & arterial patency
3- Adjuvant to thrombolytics during myocardial infarction

**Classification & Mechanisms**

**1. Drugs acting on Arachidonic acid metabolism:**
   1. **Thromboxane A\(_2\) synthesis**
      - Aspirin Small Dose (75-150 mg): selective ↓ of platelet thromboxane
      - Dazoxiben: as aspirin Small dose
      - Sulphinpyrazone: ↓ COX
      - Fish oil: abnormal thromboxanes
   2. **Prostacyclin analogue:**
      - Epoprostenol but very short t ½

**2. Drugs that ↑ c. AMP & c.GMP:**
   1. **↑ c. AMP**
      - Dipyridamol: ↓ PDE enz  \(\Rightarrow\) ↑ c. AMP
      - Pentoxiphylline: as Dipyridamol
   2. **↑ c. GMP**
      - Nitrates & Nitroprusside  \(\Rightarrow\) release (NO)  \(\Rightarrow\) ↑ G.C  \(\Rightarrow\) ↑ c.GMP

**3. Drugs acting on platelet receptors:**
   1. **Block ADP receptors** [block ADP dependent activation of GP IIb/IIIa receptors] As: Ticlopidine & Clopidogrel
   2. **Block GP IIb/IIIa receptors:**
      - Abciximab – Tirofiban – Integrelin – Eptifibatide
3) Fibrinolytics (Thrombolytics)

- **Uses:**
  They produce dissolution of blood clot (Thrombosis or Embolism) of recent onset (as in myocardial infarction or peripheral arterial thrombosis)

- **They include:**
  1) Streptokinase (Obtained from streptococci)
  2) Urokinase
  3) Tissue plasminogen activator [Alteplase]
  4) Retepase - Tenecteplase
  4) Anistreplase [APSAC]

- **Mechanism of action:** by activation of plasminogen

  Plasminogen → Plasmin (fibrinolysin) → Dissolve fibrin

**NB.:**

<table>
<thead>
<tr>
<th></th>
<th>Streptokinase:</th>
<th>Alteplase:</th>
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</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>bind to plasminogen to form a complex &amp; this complex converts Plasminogen Plasmin (fibrinolysin)</td>
<td>activate plasminogen that is bound to fibrin (it is fibrin selective)</td>
</tr>
<tr>
<td><strong>t 1/2</strong></td>
<td>&lt; 30 min.</td>
<td>&lt; 5 min.</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>1.5 million IU over 30-60 min.</td>
<td>100 mg IV (10 mg initial bolus &amp; the remaining IV infusion over 90 min.)</td>
</tr>
</tbody>
</table>

- **Side effects:**
  1- Bleeding (The most important & most common)
  2- Allergy (especially with Streptokinase)
  3- Fever

- **Contraindications:**
  1- Persistent hypertension
  2- Aortic dissection
  3- Trauma
  4- Pregnancy
  5- History of recent: surgery or cerebrovascular stroke
  6- Active GIT bleeding

**NB.: Antifibrinolysin:**
Aminocaproic acid & Tranexamic acid
Coagulants [Control of bleeding]

*Local haemostatics (stypics)*

1) Local coagulants
   1. Human fibrin (sponge)
   2. Human fibrinogen
   3. Human thrombin (powder)
   4. Human thromboplastin (powder)
   5. Oxidized cellulose (oxycel): mechanical blockage (artificial clot)
   6. Sponge gelatin

2) V.C Adr. & noradr. In epistaxis

3) Astringent tannic acid, alum precipitate blood proteins

4) Physical method: [Pressure & cold]

*Systemic coagulants:*

1) Vitamin K:
   * Used to correct bleeding from hypoprothrombinaemia that may result from:
     1. ↓ Synthesis of vit.K by intestinal flora ➔ oral antibiotics
     2. ↓ Absorption of vit. K ➔
        - Liquid paraffin - Obstructive jaundice - Malabsorption
     4. Drug induced hypoprothrombenemia ➔
        - Oral anti coagulants - Aspirin L.D.

* Sources & Preparations

1. Natural:
   - Vit. K₁ (phytonadione) orally or I.M.
     It is found in food – concentrated in liver
   - Vit. K₂ (menaquinone):
     formed by intestinal bacteria – concentrated in bone & blood vessels

2. Synthetic (more toxic):
   Menadione & Menadione di-phosphate ➔ I.M – S.C

2) Vit. C & vit. P (Rutin) ➔ used to treat capillary fragility as in bleeding gums & scurvy

3) Antihaemophilic globulin (Factor VIII): I.V to treat bleeding from haemophilia

4) Antidote for drug toxicity causing bleeding:
   1- If due to thrombolytic drugs ➔ Aminocaproic acid & Tranexamic acid
   2- If due to heparin ➔ Protamine sulphate
   3- If due to Oral anticoagulants eg.: Warfarin ➔ vit.K

5) Thromboplastin (coagulin): I.M

6) Fresh blood transfusion:

NB: Sclerosing agents
Irritant substances injected in veins of legs and piles to initiate venous thrombosis
   1) Sodium morhuate
   2) Sylnsol
   3) Sorietin

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**Hyperlipoproteinemia**

Lipoproteins are classified to:
1) Chylomicron
2) VLDL: [Containing Triglyceride > Cholesterol ester ] transporting lipids to peripheral tissue
3) LDL: [Containing mainly cholesterol ester]
4) HDL: transport cholesterol away from peripheral tissues to liver [protective]

### Drugs management of hyperlipidemia

<table>
<thead>
<tr>
<th></th>
<th>1) Statins</th>
<th>2) Fibrates</th>
<th>3) Resins</th>
</tr>
</thead>
</table>
| **Examples**   | - Atorvastatin  
- Pravastatin  
- Lovastatin  
- Simvastatin  
- Fluvastatin | - Clofibrate  
- Etofibrate  
- Fenofibrate  
- Gemfibrozil | - Cholestyramine  
- Colestipol |
| **Mechanism**  | they ↓ HMG – Co A reductase enz [rate limiting enz]  
↓ cholesterol synthesis  
compensatory ↑ in LDL receptors on hepatocytes  
↓ LDL & cholesterol | ↓ Triglycerides through :  
1. ↑ Lipoprotein lipase enz.  
2. ↓ Hepatic synthesis of T.G & VLDL | they bind with bile acid  
1- ↓ Absorption of cholesterol  
2- ↓ Absorption of bile  
↑ catabolism of cholesterol into bile acids  
compensatory ↑ in LDL receptors  
↓ LDL & Cholesterol. |
**Blood**

| Side effects | 1. Hepatotoxic \(\rightarrow\) ↑ serum transaminases  
2. Myopathy & myositis \(\rightarrow\) ↑ serum creatine kinase  
3. Contraindicated in pregnancy & lactation | 1. Hepatotoxic \(\rightarrow\) ↑ serum transaminases  
2. Myopathy & myositis \(\rightarrow\) ↑ serum creatine kinase  
3. Contraindicated in pregnancy & lactation  
4. Cholesterol gall stones & cholecystitis  
5. Displace other drugs from plasma proteins | 1. Constipation  
2. Cholesterol gall stones & cholecystitis  
3. ↓ Absorption of vit. K & other drugs e.g.: digoxin & warfarin |

(4) **Niacin**: [nicotinic acid]
   2. **Mechanism**: As Fibrates  
   3. **Side effects**:
      1. *Pruritis & flushing* due to release of PGs. Avoided by aspirin  
      2. Hyperglycemia & hyperuricemia  
      3. GIT disturbances  

**N.B Acipimox**: as niacin with less side effects.

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5) **Ezetimibe**:
   - It ↓ directly cholesterol absorption  
   - Metabolised in liver (not used in advanced liver disease)

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(6) **Probucol**:
   4. **Mechanism**: anti oxidants & ↓ cholesterol synthesis  
   5. **Side effects**:
      1. GIT disturbances  
      2. Fatal arrhythmia & long Q-T interval

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(7) **Others**:
   1. Neomycin \(\rightarrow\) as resins \(\rightarrow\) ↓ cholesterol absorption  
   2. B-Sitosterol \(\rightarrow\) as resins \(\rightarrow\) ↓ cholesterol absorption  
   3. D-thyroxin: ↑ catabolism of cholesterol into bile acids & compensatory ↑ in LDL receptors

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**N.B**: fish oil \(\rightarrow\) ↓ TG but ↑ cholesterol  
**N.B**: *Alpha tocopherol [vit.E]*:
   Has no effect on lipid level but it ↓ atheroma formation as it is a powerful antioxidant, & oxidation of LDL is essential for atheroma formation.
Antianaemic drugs

Types of anaemia

I- Deficiency anaemia. (Iron – B₁₂ – folic acid)
II- Aplastic anaemia
III- Haemolytic anaemia

I - deficiency anemia

1- Iron

Preparations:

**Oral preparation**
- Ferrous sulphate - Ferrous gluconate - Ferrous fumarate - Iron choline citrate

**Parenteral preparation**
1. Iron Dextran I.M, I.V.
2. Iron sorbitol citric acid complex I.M. only

Side effects and toxicity:

**Oral iron**
- **Gastric irritation**, colicky pain, constipation or diarrhea & black stool
- **Acute toxicity** (usually, accidentally in children):
  Manifistations:
  - Vomiting, abdominal pain, haematemesis and black or bloody diarrhea
  - Hypotension, collapse, coma, death in some cases
  Treatment:
  6. Gastric lavage with NaHCO₃ 1%
  7. Iron chelating agents: **Deferoxamine** (desferal):
     given by stomach tube - I.M. or I.V. infusion
  8. Symptomatic treatment (eg:fluids for dehydration & collapse)

**Parenteral iron preparation**

**Local toxic effect:**
- Pain at site of injection - Skin discoloration

**Systemic toxic effect (Chronic toxicity = Haemosidrosis)**
- Manifestations:
  - Headache, malaise, convulsions, fever & fainting
  - Nausea and vomiting - Muscle and joint pains, haemolysis
  - Tachycardia & Hypotension - Bronchospasm

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- Treatment:
  - Intermittent phlebotomy (every week), provided that there is no anemia
  - Parenteral Deferoxamine or Oral Deferasirox

**NB:** Iron is contraindicated in haemolytic anemia, unless haemoglobinuria is present
**NB:** Both iron & tetracycline inhibit absorption of each other

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**2- Cyanocobalamine (vit. B12) Extrinsic factor, Antipernicious anaemia factor**

The manifestations of deficiency are Pernicious anemia:
1. Macrocytic hypochromic anaemia
2. Peripheral neuritis and subacute combined degeneration

**N.B:** the primary cause for pernicious anemia is absence of intrinsic factor required for absorption of vit B12 from terminal ileum

**N.B:** Drugs that may inhibit absorption of vit. B12:
- Neomycin – PAS (para-aminosalicylic acid) - Metformin

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**Uses:**
1. Pernicious anemia and macrocytic anemia
2. Neuropathies
3. Hepatitis
4. Counteract catabolic action of cortisone

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**Preparations:**
1. Cyanocobalamine : I.M. for life 1 mg
2. Hydroxocobalamine : I.M. for pernicious anemia and cyanide poisoning

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**3- Folic acid**

**Fate:**
1. By folic acid reductase → tetrahydrofolic acid T.H.F.A. (active)
2. Both folic acid and B12 are closely interrelated

\[
\begin{align*}
B_{12} \quad & \quad \text{vit. C, } B_{12} \\
\text{Conj. Folic acid} \quad & \quad \text{free folic acid} \quad & \quad \text{T.H.F.A.}
\end{align*}
\]

**Uses:**
1) Megaloblastic anemia (nutritional and pregnancy)
2) Mal-Absorption Syndrome
3) With anticonvulsant drugs as phenobarb., primidone or phenytoin to correct associated macrocytic anaemia.

**N.B:** - In pernicious anaemia it must be given with vit. B12 otherwise neurological damage will proceed if folic a. is used alone
- Methotrexate (used in cancer therapy) is antifolic acid
**II- Agranulocytosis / Aplastic anaemia**

**Causes:**
1) Analgesic → pyrazolone eg.: (Dipyrone)
2) Antithyroid → thiouracil
3) Antibacterial → chloramphenicol and sulphonamide
4) Antiepileptic → Trimethadione
5) Antineoplastic drugs (Cytotoxic drugs)
6) Gold
The early manifestation of agranulocytosis is *sore throat*

**Treatment:**
1) Stop the cause
2) Blood transfusion
3) Vit. B₁₂ and folic acid, vit.C
4) Haemopoietic growth factors
5) Antimicrobial for infections

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**Met-hemoglobinaemia**

It is the conversion of Fe⁺⁺ of haemoglobin into Fe⁺⁺⁺

**Causes:**
1. Phenacetine
2. Nitrite
3. Sulphonamides
4. Primaquine

**Treatment by:**
1. Methylene blue
2. Vit. C “ascorbic acid”

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**Hematopoietic growth factors**

Developed using recombinant DNA technique and include:

1. **Erythropoietin:** produced primarily by renal cortex, used mainly in treatment of anemia due to chronic renal failure. But can be used also in AIDS and in anemia of cancer therapy.
2. **Thrombopoietin** is a cytokine that increases platelet count when combined with other growth factors.
3. **Granulocyte / macrophage colony- stimulating factor (GM-CSF):** used to stimulate myelopoiesis in AIDS, aplastic anemia and cancer chemotherapy.
4. **Granulocyte colony- stimulating factor (G-CSF)** is used to treat severe neutropenia following bone marrow transplantation or cancer chemotherapy.
5. **Interleukins** (IL 1, 3, 5, 6, 9, 11) act synergistically with stem cell factor (SCF), GM-CSF, G-CSF and erythropoietin.