Drugs used in treatment of anemia:

1- ***Iron***: Iron deficiency is the most common cause of chronic anemia.

Causes of iron deficiency: 1- increased requirements 2- inadequate absorption
3-blood loss (the most common cause).

Oral iron preparations:

- Fe-sulfate, Fe-gluconate, Fe-fumarate.

➔ Side effects: nausea, cramps, discomfort, constipation or diarrhea with black stools.

Parenteral therapy:

- Iron dextran → deep IM injections → causes local pain and tissue staining.
  → IV infusion → causes hypersensitivity rxn.
- Iron sucrose complex: given IV.
- Iron-Na gluconate: given IV, less likely to cause hypersensitivity.

➔ Side effects to parenteral therapy: risk of iron overload.

Iron toxicity:

1) Acute iron toxicity: either due to accidental ingestion by children (10 tablets can be lethal) or due to parenteral iron therapy.

Oral administration might cause necrotizing gastroenteritis [vomiting, pain, bloody diarrhea, shock, lethargy, dyspnea], patients may improve but may proceed to metabolic acidosis, coma and death.

Treatment: deferoxamine (desferal), whole bowel irrigation, supportive therapy.

2) Chronic iron toxicity (aka hemochromatosis): occurs in hemolytic anemia patients who require frequent transfusions, or could be inherited (increased absorption of iron)

Leads to organ failure (heart, liver, pancreas).

Treatment: intermittent phlebotomy (in inherited cases), deferoxamine, deferasirox (orally).

2- ***Vitamin B12***: Has 3 actions:

- Conversion of N5-methyltetrahydrofolate to tetrahydrofolate.
- Conversion of homocysteine into methionine.
- Isomerization of methylmalonyl-CoA to succinyl-CoA by the enzyme methylmalonyl-CoA mutase.

If Vitamin B12 is deficient it leads to:

-Accumulation of methyl tetrahydrofolate: this is corrected by ingestion of folic acid because folic acid can be reduced to dihydrofolate by the enzyme dihydrofolate reductase.

-Accumulation of methylmalonyl-CoA: leads to neurological manifestations.

Therapy with Vitamin B12:

- Parenteral (life-long): injection every day or two for 1-2 weeks and maintenance every 1-4 weeks.
- Oral.
- Intranasal: For patients in remission.

3- ***Folic acid:*** Has 3 actions:

- Production of dTMP from dUMP, which is needed in DNA synthesis.
- Generation of methionine from homocysteine: folic acid deficiency causes occlusive vascular disease (e.g. atherosclerosis, cerebrovascular and coronary disease) due to elevated homocysteine.
- Synthesis of essential purines.

Causes of megaloblastic anemia of folic acid deficiency: 1- Inadequate dietary intake.

2- Alcoholism. 3- Liver disease. 4- Pregnancy and hemolytic anemia. 5- Malabsorption syndrome. 6- Renal dialysis. 7- Drugs: Methotrexate, Trimethoprim, Phenytoin.

Treatment with Folic Acid:

- Oral supplements (1mg daily).
- Prophylactic for pregnant ladies
- Parenteral administration is rarely necessary because it is well absorbed orally (even in malabsorption).

Drugs used in thromboembolic disease:

- ➔ Risk factors for thromboembolism: 1- Abnormalities of Blood Flow. 2- Abnormalities of Surface Contact with blood. 3- Abnormalities of Clotting Components.

- ➔ Non Thrombogenic Mechanisms in Blood Vessels: 1- Transmural negative electrical charges.

2- Plasminogen activation 3- Protein C activation. 4- Production of heparin-like proteoglycans.
5- Release of PGI2.

1) Indirect thrombin inhibitors

-**Heparin**: mixture of sulfated mucopolysacharides.

Composed of sulfated glucosamine **+** D-glucuronic acid connected by sulfaminic bridges.

$T_{1/2}$= 1h, distribution only to IV compartment, doesn't cross the placenta and is not excreted in breast milk.

Rapidly metabolized by heparinase enzyme in the liver, renal excretion and uptake by the RES.

MOA: acts in peripheral blood where it increases the electronegative potential of the vessel wall, causes release of tissue factor pathway inhibitor (TFPI), inhibits platelets aggregation, activates lipoprotein lipase (reduces platelets adhesiveness), binds to antithrombin-III and causes conformational changes exposing the active site to proteases (esp thrombin, IXa, Xa) accelerating this interaction.

- ➢ Unfractionated heparin (UFH or High molecular weight heparins, HMWHs): 2/3 MW of heparin, bind with high affinity to antithrombin.
- ➢ Low molecular weight heparins (LMWHs): cause factor Xa inhibition. Compared to HMWHs they have equal efficacy, less dosing requirements, higher bioavailability, more predictable effects, doses in mg rather than units, only require monitoring in renal failure, pregnancy and obesity.

Monitoring for UFH by: activated partial thromboplastin time (aPTT), protamine titration and anti-Xa units.

Toxicity with heparin leads to: bleeding, thrombocytopenia, alopecia, allergic rxn, osteoporosis, mineral corticoid deficiency.

Contraindicated in thrombocytopenia, hypersensitivity, active bleeding, severe HTN, active TB, ulcerative lesions, threatened abortion, carcinoma, liver/renal disease.

-Administration of UFH: initial bolus, continuous infusion through a pump, SC for low dose prophylaxis.

To reverse toxicity give antidote → protamine sulfate.

-Administration of LMWHs: SC → completely absorbed, once or twice daily.

If monitoring is required, perform Xa inhibition assay.

No antidote available nor needed.

-**Fondaparinux:** synthetic pentasaccharide fragment of heparin.

$T_{1/2}$= 15h , binds antithrombin and results in more selective inactivation of factor Xa.

2) **Direct thrombin inhibitors:**

-Hirudine -Lepirudin -Bivalirudin

These are bivalent compounds, they bind at both the catalytic site and the substrate recognition site of thrombin. Eliminated by kidneys.

Side effects: allergy and anaphylaxis.

-Argatroban -Ximelagatran -Melagatran

Small molecules that bind only at the active site of thrombin. Eliminated by the liver.

3) **Factor Xa inhibitors:**

-Rivaroxaban -Apicaban -Edoxaban

These inhibit factor Xa, in the final common pathway of clotting. Given orally at fixed doses, don't require monitoring. Used to prevent stroke in atrial fibrillation.

4) **Oral anticoagulants**

-Bishydroxycoumarin: caused hemorrhage in cattle, initially used as rodenticides, still very effective more than strychnine.

-Warfarin: bioavailability= 100%, peak within 1h, 99% bound to proteins (small volume of distribution and long half-life), doesn't cross the BBB, crosses the placenta, hydroxylated in the liver.

MOA: acts in the liver not in the circulation. Blocks γ-carboxylation → no synthesis of factors II,VII,IX,X as well as proteins C and S. Warfarin also prevents the reductive metabolism of inactive Vit. K epoxide.

Effect results from a balance between: 1) partially inhibited synthesis AND 2) unaltered degradation of the four Vit. K dependent clotting factors.

Its action starts after 48h (DO NOT increase the dose).

Given in small doses (5-10mg), resistance in cancer patients, monitored by prothrombin time (PT) and international normalized ratio (INR).

Toxicity: bleeding, teratogenicity, cutaneous necrosis, infarction of breast ,fatty tissues, intestine and extremities.

Toxicity reversed by Vit. K, fresh-frozen plasma, prothrombin complex concentrates, recombinant factor VII.

5) **Fibrinolytic agents:** they catalyze the formation of plasmin from plasminogen → rapidly lyse thrombi.

Indications: Pulmonary embolism, DVT, ascending thrombophlebitis, Acute MI.

-Streptokinase (not fibrin-specific → bleeding), highly antigenic so it causes allergic rxns and inactivation of the drug. Early administration is important.

-Urokinase (human enzyme synthesized by the kidneys), not antigenic, expensive.

-ASPAC (Anistreplase): deacylated at fibrin surface → release of active complex. More active and selective, $t_{1/2}$=6h

-Tissue plasminogen activators (Ateplase, Reteplase, Tenecteplase)

Synthesized by the endothelial cells, specific action within the thrombus, activates plasminogen at the fibrin surface. $T_{1/2}$= 8 min, given by infusion over 1-3h, <u>very expensive.</u>

6) **Antiplatelet drugs**

Types of platelet regulators: 1- Agents generated outside platelets which interact with membrane receptors (collagen, thrombin, prostacyclin).

2- Agents generated inside and interact membrane receptors (ADP, PGD2,PGE2,serotonin).

3- Agents generated within and interact within platelets (TX-A2, cAMP, cGMP, Ca).

Platelets adhesion and aggregation:

- **GPIa/IIa and GPIb:** they bind collagen and vWF causing adhesion of platelets to the subendothelium.
- **P2Y1 and P2Y12:** these are ADP receptors, when stimulated they activate GPIIb/IIIa and COX-1 causing platelet aggregation and TX-A2 production.
- **PAR1 and PAR4:** protease-activated receptors that respond to thrombin.
- **Prostacyclin (PGI2):** inhibits platelet activation.

TXA-2	*PGI2*
1- vasoconstriction	*1- vasodilation*
2- platelet aggregation	*2- platelet disaggregation*
**enhances clotting*	**Prevents clotting*
**produced by COX-2 in the platelets*	**produced by an enzyme in the endothelium*

Antiplatelet drugs:

-COX-1 inhibitors (Aspirin): irreversibly acetylating COX-1, reduced TX-A2 synthesis (PGI2 production is not affected), $t_{1/2}$= 7-10 days.

-Ticlopedine (Ticlid), Clopidogrel (Plavix) and Prasugrel: irreversibly block P2Y12 (whereas cangrelor and ticagrelor are reversible inhibitors of P2Y12).

Used in TIAs, strokes, unstable angina, after placement of coronary stents.

SE: leukopenia, GI irritation, skin rash.

-Abciximab (monoclonal Ab of GPIIb/IIIa), Eptifimeide (synthetic peptide), Tirofiban.

All inhibit binding of fibrinogen and vWF to GPIIb/IIIa.

- Dipyridamole, Cilostazole: they inhibit adenosine uptake and phosphodiesterase enzyme (↑ cAMP), they also work as vasodilators.

-SCH30348 and E555: PAR1 inhibitors.

-Dazoxiben: inhibits TX synthetase enzyme.

-Sulotroban: inhibits TXA2 receptor.

-Anagrelide: reduces platelet production by reducing megakaryocyte maturation.

-Lipid lowering agents.

7) **Hemostatic agents**

Whole blood, fresh frozen plasma, plasma fraction, Vit. K, absorbable gelatin foam, absorbable gelatin film, oxidized cellulose, thrombin.

8) **Plasmin inhibitors** (they inhibit bleeding in patients with bleeding tendency)

- Alpha-2 Antiplasmin.

- Aprotinin.

- Aminocaproic Acid.

- Tranexamic Acid.

[Both hemostatic agents and plasmin inhibitors induce clotting]

Hematopoietic growth factors

1) **Erythropoietin (EPO)**

Recombinant human erythropoietin (rHuEPO, or Epoietin alfa) is produced in a mammalian cell expression system.

- Given IV, $t_{1/2}$= 4-13h, not cleared by dialysis. Darbepoetin alfa has longer half-life.
- Needs active(responsive) bone marrow (no iron/folic acid/ Vit.B12 deficiency).

- Elevated in most anemias (except in anemia of chronic renal failure).
- Interacts with JAK/STAT cytokine receptor, causes release of reticulocytes from BM.

Uses: -Anemia of chronic renal failure (IV or SC) → Failure to respond is usually due to iron or folic acid deficiency.

-Primary BM disorders and secondary anemias (require higher doses).

-Anemia of zidovudine treatment. –Anemia of prematurity.

-After phlebotomies. –Iron overload.

Toxicity: HTN, thrombotic complications, allergic rxns (mild and infrequent).

2) **G-CSF**

rHuG-CSF (*Filgrastim*) is produced in a bacterial cell expression system.

- Pegfilgrastim= Filgrastim covalently conjugated with polyethylene glycol (injected once per chemotherapy cycle).
- $T_{1/2}$= 2-7h.
- Works on JAK/STAT receptors, stimulates proliferation and differentiation of progenitors committed to the neutrophil lineage.

3) **GM-CSF**

rHuGM-CSF (*Sargramostim*) is produced in a yeast cell expression system.

- $T_{1/2}$= 2-7h.
- Also works on JAK/STAT receptors, it stimulates proliferation and differentiation of early and late granulocytic progenitor cells as well as erythroid and megakaryocyte progenitors.
- With IL-2, it also stimulates T-cell proliferation.

Uses of G-CSF and GM-CSF:

- Chemotherapy-induced neutropenia (reduces episodes of febrile neutropenia, need of antibiotics and days of hospitalization), they do NOT improve survival.
- Congenital and cyclic neutropenia.
- Myelodysplasia. – Aplastic anemia. –Autologous stem cell transplantation.
- Allogenic BM transplantation. –Mobilization of peripheral blood stem cells.

Toxicity of G-CSF and GM-CSF: bone pain, fever, myalgia, capillary leak syndrome, allergic rxn, splenic rupture.

4) **Megakaryocyte growth factors**

- IL-11: Produced by fibroblasts and stromal cells in the bone marrow.

$T_{1/2}$= 7-8h after SC injection.

- Acts through a specific receptor, stimulates the growth of multiple lymphoid and myeloid cells, stimulates the growth of primitive megakaryocytic progenitors, Increases the number of peripheral platelets and neutrophils.
- Uses: Thrombocytopenia (platelets transfusion is an alternative), no effect on leukopenia, SC injection after chemotherapy.
- Oprelvekin: the recombinant form of IL-11 (produced by expression in E.coli).

- Thrombopoietin:

- Recombinant form is produced by expression in human cells.
- Actions: stimulates the growth of primitive megakaryocytic progenitors, stimulates mature megakaryocytes, activates mature platelets to respond to aggregation-inducing stimuli.

Toxicity: Fatigue, headache, dizziness, anemia, dyspnea, transient atrial arrhythmias and hypokalemia.

Antimalarial agents

-Chloroquine (4-aminoquinolone), accumulates in food vacuoles of the parasite, inhibits the polymerization of heme into hemozoin → toxicity by heme.

- Well absorbed, distributed, bound to tissues, rapid action, low cost, safe.
- Destroys all blood stages of all 4 types of malaria.
- Drug of choice in the treatment of nonfalciparum and sensitive falciparum malaria.
- Does NOT eliminate dormant liver forms of P. vivax and P. ovale (Primaquine must be added). Resistance in P. falciparum and P. vivax.
- Also used in: rheumatoid arthritis, LE, Amebic liver abscess, photogenic rxns, Clonorchis sinensis.
- SE: headache, dizziness, itching, rash, N+V, anorexia, unmasking of LE, psoriasis, porphyria, corneal deposits, blindness, blurry vision.

Common SE for all cancer drugs:

Alopecia, Immunosuppression, BM suppression, Oligospermia, GI manifestations.

Treatment of leukemias:

1) ALL

- Most common leukemia in children (80% of leukemias in children, 80% completely cured).
- Death within 2-3 months if left without treatment.
- Can be cured with drugs only → if relapses occur then BM transplantation is required.
- Manifestations of ALL: immunosuppression, anemia, bleeding, infections.
- Goal of therapy is to reach complete remission (CR) first, then leukemia free survival (cure).
- Stages of therapy:

➢ *Induction*: the goal is to induce CR, characterized by tumor lysis syndrome (because we induce a very high number of the cancerous cells to commit apoptosis, these cells will secrete their contents in the blood → many manifestations including hyperuricemia and kidney failure).
High doses of:
Vincristine (mitotic spindle inhibitor) → SE: peripheral neuropathy.

+ Glucocorticoids [prednisone] (antiproliferative) → many SE.

+ L-asparginase (destroys Asparagine) → SE: hyperglycemia, edema, hemolysis or thrombosis.

➢ *Consolidation (intensification)*: (4-6 months)

Either we give higher doses of L-asparginase.

Or

We change the drug → give methotrexate and 6-mercaptopurine (both are antimetabolites).

After consolidation, a BM biopsy should show no leukemic cells.

➢ *CNS prophylaxis*: in 60% of cases, malignant cells escape to the brain producing leukemia in the brain (meningeal leukemia), so CNS prophylaxis is a must!
In **adults**: high doses of methotrexate, cytarabine, L-asparginase **systemically**.
In **children**: methotrexate, cytarabine, steroids **intrathecally**.

➢ *Maintenance*: to make sure no single cancerous cell will come back.
3 years for boys and adults, 2 years for girls.
Methotrexate weekly and 6-mercaptopurine daily.

2) **AML**

- Can't be cured with drugs, we have to do BM transplantation.
- More resistant to treatment, most cases we won't reach to CR.
- Stages of therapy:

- *Induction*:
  Anthracycline (Daunorubicine): topoisomerase inhibitor, for 3 days → SE: cardiac toxicity.
  Cytosine arabinose (Ara-C): antimetabolite, for 7 days → SE: ataxia, dizziness.
  Both drugs cause BM suppression → Pancytopenia.
- Either give the drugs but in higher doses for 4-6 weeks (consolidation)
  Or
  BM transplantation (more effective) → 50-60% cure

NO NEED FOR CNS PROPHYLAXIS

3) **CML**: treatment by imatanib (tyrosine kinase inhibitor of BCR-ABL fusion gene in Philadelphia chromosome).

4) **CLL**: survival rate of approximately 10 years.

- Watch and wait until symptoms appear, no survival advantage of treating the disease too early.
- Low risk CLL: give single oral agent → low dose of Fludarabine or Chlorambucil or Rituximab.
  Fludarabine is an antimetabolite, stronger agent and has more aggressive SE (immunosuppression, increased risk of infections, hemolytic anemia). Given if the patient is <65y.
  Chlorambucil is an alkylating agent, mild SE. Given if the patient is >70y.
  If no response to any of the agents → give Rituximab (anti -CD20 Ab).
- Intermediate risk CLL:
  Fludarabine + Rituximab OR Cyclophosphamide + Rituximab
- High risk CLL:
  Fludarabine + Rituximab cycles with BM transplantation.

Treatment of Lymphomas:

1) **Hodgkin's lymphoma** (characterized by Reed-Sternburg cells), 10 year survival=80%, most cases are curable.

- If one LN involved (low stage) → treated by radiotherapy
  If more than one LN involved → Chemotherapy
  More than that and spleen involvement (aggressive) → high dose chemotherapy and radiotherapy.
- Regimen for Hodgkin's lymphoma: **ABVD**

Adriamycin (topoisomerase inhibitor)
Bleomycin (Intercalation and iron chelation)
Vinblastine (Mitotic spindle inhibitor)
Dacarbazine (Antimetabolite)
SE: Secondary malignancy (leukemia, NHL), Solid tumors (lung, breast), Infections, Cardiac (Adriamycin), pulmonary (Bleomycin) and endocrinal abnormalities.

2) **Non-Hodgkin's lymphoma**: more common than HL. Affect males more than females, and the median age of presentation is 65-70 years. B cells 70% , T cells 30%.
Classified into:
- Indolent form: long natural history, slow cellular accumulation, incurable with drugs, control is the goal of treatment.
- Aggressive form: short natural history, rapid cellular proliferation, curable (50% chance), cure is the goal.

Treatment of the aggressive form: **R-CHOP** (6 cycles, every 3 weeks).
Rituximab (anti-CD20 Ab) → without it patients only reach 50% of CR → SE: fever, chills, drop in BP, dyspnea.
Cyclophosphamide → SE: cystitis
Doxorubicin **H**ydrochloride → SE: cardiac toxicity
Oncovin (Vincristine) → SE: peripheral neuropathy
Prednisolone → many SE (those of corticosteroids)

[Other than Rituximab, other monoclonal antibodies can be used, like: Obinutuzumab, Ofatumumab, Epratuzumab and Lucatumumab].

MOA of antibody-based drugs:
1- They either induce apoptosis of cancerous cell.
2- They're modified by attaching it to a toxin or an antibiotic.
3- They sensitize other immune cells to kill the cancerous cell.

Modifications on Abs:

1- Bispecific T cell engager: two Abs used, one binds to the cancerous cell, the other binds to a killer cell.

2- Ab-drug conjugate:

Ex: Vedotin-bound Ab.

Myeloid growth factors: (G-CSF and GM-CSF)

- Used for neutropenia induced by chemotherapy.
- *G-CSF*: given in cases of AML due to the use of high doses of Ara-C.
  Mutation in its receptor results in congenital neutropenia.
  Recombinant form → Filgrastim
  SE: Splenomegaly (spleen rupture), Bone pain (in 30% of cases).
- *GM-CSF*: increases the production of neutrophils and macrophages.
  Used to reduce the risk of death due to infections in patients >55 undergoing induction chemotherapy.
  Also used in strong cancers like AML and breast cancer.
  Recombinant form → Sargramostim
- *Febrile neutropenia*: fever, chills, neutropenia
  Managed by giving broad spectrum antibiotics like Carbapenems (Imipenem -Tienam-), myeloid GFs and Abs.

- *BM transplantation*: allogenic vs Autologous

- *Vaccination*: collect the patients T-cells and expose them to antigens in vitro, then reinject them into the patient.

➔ On the side: EPO is given for: 1-chemotherapy induced anemia 2-pateints who require BM transplantation 3-those who suffer from kidney failure.

➔ For thrombocytopenia we give IL-11 or Thrombopoietin or fresh frozen plasma.