Normal hemoglobin(HB) concentration=13-15g/dl

Anemia

A blood disease leading to decrease blood hemoglobin concentration below normal value

Mild anemia: HB 10-13

Moderate anemia :HB 5-10 g/dl

Severe anemia: HB=below 5 g/dl

Causes of anemia

Deficiency

-Iron deficiency caused by *Decrease GIT absorption of iron *Sideroplastic anemia: Defective iron utilization in alcoholics

-**Folic acid and Vitamin B12 deficiency**

-**Vitamin B6 &B1 deficiency rare**

-Trace element(cupper) deficiency.

Hemolytic :Excessive RBC destruction

Intravascular inside blood vessels by

Toxins : lead , arsenic

-Autoimmune antibodies in autoimmune hemolytic anemia, systemic lupus,rheumatoid arthritis

-Burns.

-Severe exercise : Running

-Drugs (oxidizing agents) parcetamol,chloroquine , sulfonamides ,dapason quinine , quinidine, vitamin k especially in patients with g-6-phosphate dehydrogenase deficiency

-Acute iron overdose

-Prosthetic valves :artificial valves

-Complement induced hemolysis:

*Paroxysmal nocturnal hemoglobinurea ,

*Atypical hemolytic uremic syndrome

Extravascular in spleen &Liver caused by

1 -RBC defects

*RBC wall defect : spherocytosis

*HB defect: Thalassemia (HBF)

*Natural antioxidant defect : glucose 6 dehydrogenase deficiency. Hemolysis is manifested after intake of oxidizing agents eg drugs (chlorquine ,quinine quinidine ,paracetamol , methyldopa sulfonamide , dapson,

Aplastic defect in blood cell production

1-marrow failure

Caused by :

-Chronic infections

-Drugs: anti-cancer , antiepileptic (phenytoin& caramazipine)

-Chloramphicol

-Antiviral drugs (zidofudine)

-Irradiation

-Infiltration of bone marrow by blast cells in cases of leukemia

-Autoimmune aplastic anemia lymphocytes attack and destroy bone marrow cells

Morphological types of anemia

Microcytic (small cell) anemia

Iron &Vitamin B6 deficiency & lead induced &thalathemia & some cases anemia of Chronic infections .RBCS contain less HB

Macrocytic (Large blood cell) anemia

-Folic acid & vitamin B12 deficiency, aplastic anemia , hypothryrodism due to delay in RBC division

-Hyperactive bone marrow releases of immature RBCs in chronic ,lung diseases , hemolytic anemia , malaria , mechanical RBC destruction (prosthetic valves)

Normocytic normal size but less number of RBCS in other types of anemia

Causes of iron deficiency anemia

1-Chronic blood loss excessive menstruation ,chronic GIT bleeding (ulcers , hemorrhoids , inflammatory bowel diseases, some parasitic diseases eg bilharzia and Encylostoma)

2-Decrease iron absorption as in cases of mal-absorption syndrome or drugs (tetracycline , phosphate , phytate (bran), antacids , drugs that decrease gastric HCl secretion in patients with peptic ulcer)

3-Increase iron demands as in cases of

- Delayed weaning of children because breast milk is deficient in iron .
- Pregnancy.
- Premature baby due to decrease iron stores derived from the mother
- During treatment of pernicious (vitamin B12 &folic acid deficiency) anemia due to excessive formation of new RBCs .

Clinical picture of anemia

.Decrease RBCs leads to fatigue, pallor in skin and mucous membranes-1

Deficiency in iron containing enzymes leading to degeneration of mucous membrane in tongue (glazed tongue with loss of-2 . papillae)tonsils and atrophy of epithelial cells in skin and GIT

.Decrease immunity leading to increase susceptibility to infections. especially helminthic infections-3

Indications of iron therapy

- Iron deficiency anemia.
- Prophylactic against iron deficiency anemia as a result of increased iron demands (pregnancy and premature babies).
- During treatment of other causes of anemia (increase iron demand as a result of excessive formation of new RBCs.)

Preparations of oral iron

.Ferrous sulfate contains 60 mg of iron/tablet-

.Ferrous fumarate contains 65 mg of iron/table -

.Ferrous gluconate &succinate contains 35 mg of iron/tablet-

.Ferrous editate and elemental iron .They are tasteless .They are used to fortify milk-

. Dose:200 mg (2tablets three times daily) or 2-3 mg/kg for adults and 5mg /kg for children .it increases HB by 0.2 g/day

.Iron should be administrated till serum hemoglobin is normalized followed by1-2 months to replenish iron stores-

-If there is continuous iron loss ,administrate iron in a dose of 20 mg /6 hours till the cause of iron loss is treated.

-Drugs that increase iron absorption :Acids (vitamin c , citrates , succinates) , sulfur containing amino acids (SH group reduces ferric to ferrous ions) are combined with iron therapy.

Side effects

.Dose dependent due to direct effect of iron :nausea ,vomiting and upper GIT upset-1

Dose independent due to decrease bacterial flora :indigestion ,diarrhea or constipation-2

Indications for parenteral iron:1-Non compliant patients who refuse to take oral iron therapy.
.Malabsorption syndrome as in cases of inflammatory bowel syndrome or surgical resection of large part of intestine-2
3-When iron deficiency should be compensated rapidly as in cases of pregnancy or before surgical operations.
Preparations of parenteral iron-Iron sorbitol .It is rapidly absorbed .It can be given both intravenously and intramuscularly.
-Iron dextran .It is slowly absorbed. It can be given slowly intravenous or intramuscular
Dose of parenteral iron: Total dose of iron =iron deficit in grams X 250 or deficit in % X 3 X body weight. It is administrated intravenous infusion in 5% glucose solution (maximal concentration is 2.5 g iron /liter.
.Initial test dose 0.0.5 ml of the solution is first administrated over 3 minutes to test for of anaphylactic shock
Intramuscular iron is administrated by Z technique (move skin upwards before injection)to avoid skin staining. It may cause-sarcoma at the site of injection
:**Side effects of parenteral iron**
.Systemic: Anaphylactic shock ,Headache and Lymphadenopathy
Local :tissue staining and malignancy (sarcoma at the site of IM injection).

Acute iron toxicity

-Due to suicidal or accidental intake of large doses of iron .It is manifested by

- GIT manifestations : vomiting ,abdominal pain and bloody diarrhea.
- Cardiovascular manifestations : Metabolic acidosis ,collapse
- CNS manifestations : coma and convulsions
- Hematological :hemolysis.

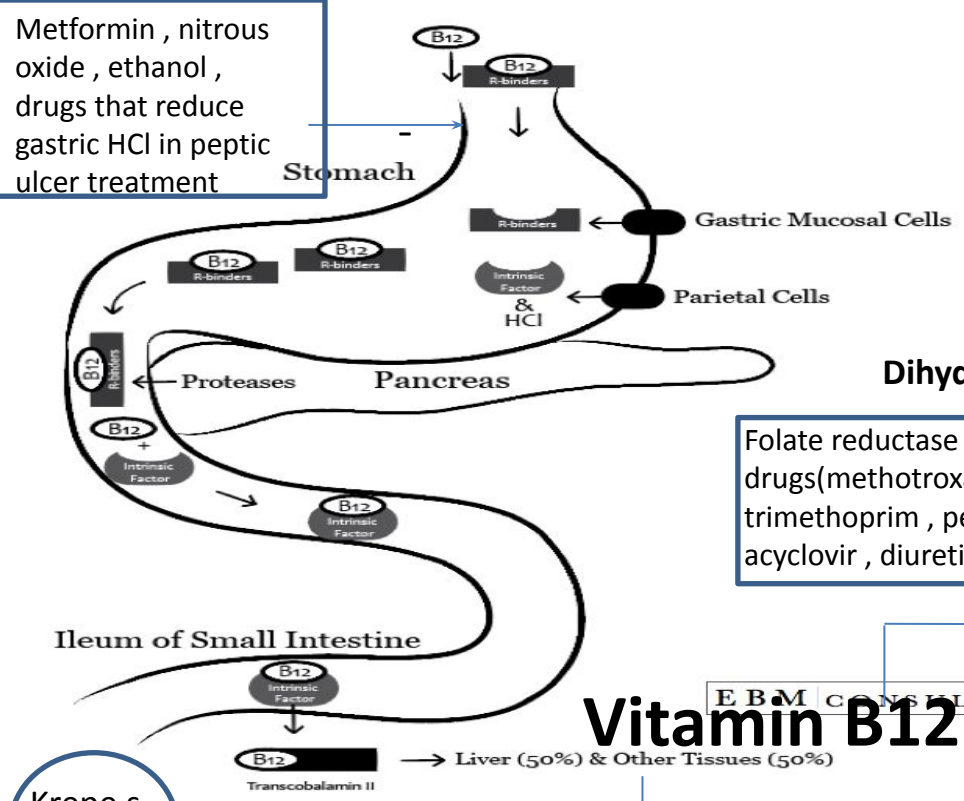
Treatment
-Decrease iron absorption by:

- Administration of milk or row egg white.
- Gastric lavage by alkaline solution eg 1% sodium bicarbonate .
- Iron chelating agents 5 g desferroxamine infusion is left in the stomach after gastric lavage.

.Chelating plasma iron by desferroxamine 1-2 g intramuscular or 15 g/kg intravenous-
.Correct acidosis by intravenous infusion of alkaline salt (sodium bicarbonate or 1/6 molar sodium lactate)-
Chronic iron toxicity (hemochromatosis):-Due to congenital defect in iron absorption or repeated blood transfusion in patients who do not bleed (agranulocytosis or severe anemia).
-It is manifested as tissue iron deposition , liver cirrhosis , heart failure , impotence and hemolytic anemia).
Treatment :-Repeated venesection 500 ml /week.
. Iron chelating agents :intramuscular desferoxamine 1-2 g/day-
.NB: iron therapy and iron rich dietary products are contraindicated in liver diseases due to iron induced hepatotoxicity

Vitamin B12	Folic acid	Iron	
Colonic bacterial flora as s-adenosy- or methyl cobalamine . Dietary sources :Liver , kidney , meat , fish	Egg , meat, milk as folate polyglutamate	-Liver , spleen , meat as F++ in HB	Dietary source
-it needs vitamin R binder secreted by salivary glands & intrinsic factor secreted by gastric mucosa	Folate polyglutamate is converted to folate mono-glutamate by glutamyl transferase -Transported with H+ by active transporter and P protein	-Ferrous ion of animal origin (HB in liver & spleen) -Ferric ion needs reduction by gastric HCL , sulfur containing amino acids or vitamin c	GIT absorption
Hydroxycobalamine bound with transcoplamine II	Dihydrofolate monoglutamate Bound with folate binding protein	F++ binds with transferritin	Transport in plasma
-Vitamin B12 is converted to hydroxycobalamine which is stored in bound form with transcoblamine III in liver	Dihydrofolate monoglutamate	Ferritin (available for RBCs)& hemosiderin (inactive ferritin aggregate)	Storage
-Activation of tetrahydrofolate to N methelene tetrahydrofolate by homocystine methyl transferase -Synthesis of odd number fatty acids required for myline sheath by methyl malonyl coA isomerase enzyme	-Transfer of methyl group used in: *Conversion of uracil to thymine *Synthesis of amino acids	-Formation of iron containing compounds (HB ,myoglobin , respiratory enzymes	Functions
-Megaloplastic anemia(pallor , dyspenia) -Peripheral neuritis & degeneration of posterior column tract in spinal cord (sub-acute combined degeneration)	-Megaloplastic anemia (pallor , dyspenia) -Decrease platelets and WBCS	-Pallor , dyspnea -Atrophy of tongue pappilae & mucous membranes &skin	Clinical picture of deficiency
Decrease GIT absorption : ***Mal-absorption syndrome, *Drugs (ethanol , antiepileptic drugs antacids ,drugs that decrease gastric HCL , metformin , nitrous oxide * obesity gastric bypass surgery *Decrease synthesis of intrinsic factor :congenital , stomach diseases (atrophic gastritis, cancer stomach) **Excess consumption : * Diphylobotherium infestation *Increase demand during treatment of other forms of anemia	**Decrease absorption**:-Mal-absorption syndrome & antiepileptic drugs ethanol **Increase demand**: pregnancy, treatment of other forms of anemia **Impaired activation** by vitamin B12 in cased of vitamin B12 deficiency -Folate reductase inhibitors (trimethoprim , anticancer(methotroxate , 5flurouracil), antiviral (acyclovir ,	**Increase demand in** pregnancy & pre-mature baby & during treatment of other types of anemia , late weaning & chronic blood loss **Decrease GIT absorption** (phytate ,	Causes of deficiency

Vitamin B12



Krepe s cycle → Succenyl coA → Methylmalonyl CO A → Odd number fatty acids → Myline sheath

Causes of vitamin B12 deficiency

1-Decrease GIT absorption : *Mal-absorption syndrome,

*Drugs (metformin (antidiabetic) , nitrous oxide , drugs that reduce gastric HCL in treatment of paptic ulcers)

*Surgery that removes part of stomach or small intestine (obesity surgery)

*Decrease synthesis of intrinsic factor :congenital , stomach diseases (atrophic gastritis, cancer stomach)

2-Increase consumption : *Parasitic infections (diphylobotherium).

*Increase demand during treatment of other forms of anemia

3-Decrease synthesis by intestinal flora: long term use of broad spectrum antibiotics which inhibit commensals and increase fungi which consumes vitamin B12

Inactive Di-hydro- Folic acid poly-glutamate in diet

Small intestine γ glutamyl hydolase

Antiepileptic drugs :phenytonin , barbiturates) , ethanol , antacids drugs of peptic ulcer treatment

H+ **Dihydrofolic acid mono-glutamate**

Active transporter

Intestinal epithelium

P-glycoprotein

Dihydrofolic acid mono-glutamate-binding protein in plasma

Di-hydro-folic acid in tissues

Folate reductase inhibitors :anticancer drugs(methotroxate) ,5fluro-uracil, trimethoprim , pentamidine , zidofudine , acyclovir , diuretic (triametrine

Folate reductase enzyme

Tetra-hydrofolic acid

Homosystine (methyl donor)

Homocystine methyl transerase

systothionine

Active N -methelene tetra-hydro-folic acid

Uracil → thymine → DNA

Rapidly dividing cells

Causes of folic acid deficiency

1-Decrease absorption:-Mal-absorption syndrome & antiepileptic drugs (phenytoin & barbiturates), ethanol

2-Increase demand: pregnancy, treatment of other forms of anemia

3-Impaired activation by vitamin B12 in vitamin B12 deficiency

-Folate reductase inhibitors (trimethoprim , anticancer(methotroxate , 5flurouracil), antiviral (acylovir , zidofudine), anti-protozoal (Pentamidine, pyrimethamine) ,

Therapeutic uses of folic acid

1-Treatment of pernicious anemia due to folate deficiency in combination with vitamin B12 in order to activate folate

2-Prophylactic in conditions associated with increase folate demands in cases of :

- Pregnancy .It may reduce the risk of congenital anomalies of nervous system.
- Premature babies
- During treatment of other types of anemia (hemolytic anemia) due to active bone marrow
- Treatment of drugs that interfere with absorption or activation of folic acid .

3-Poor intake of folic acid (old age , severe illness , starvation or prolonged malnutrition or poor appetite in depression

4-Bleeding hypertrophied gum : folic acid is required for activation of metalloprotease and collagenase enzymes required for collagen turnover in gums and other tissues

Preparations of folic acid

Dihydrofolic acid (FH2) 3 times/day. It is given orally .It needs activation to methylated tetrahydrofolic acid by vitamin B12.

- Active Follinic acid (formyl tetrahydrofolic acid)is used in combination with folate reductase inhibitors to prevent anemia.

Side effects of folic acid preparations

1-Allergic reactions (skin rash , bronchospasm , itching) due to hypersensitivity reactions to drug solvents.

2-Very large doses may cause gout due to increase formation of nitrogenous bases which are metabolized to uric acid.

3-Large doses of folic acid alone in pernicious anemia caused by either deficiency of folate or vitamin B12 may cause consumption of vitamin B12 in activation of folic acid and appearance of nervous side effects of vitamin B12 deficiency

Therapeutic uses of vitamin B12(hydroxycobalamine & cayanocobalamine)

1-Treatment of vitamin B12 deficiency anemia initial dose of 1000 ug /month till the blood picture is normalized then it is administrated in a dose of 1000 ug /1-3 months for life.

2-In combination with folic acid in treatment of folic acid deficiency anemia to promote folic acid activation.

3-Treatment of peripheral neuritis and degenerative conditions of nervous system mediated by vitamin B12 deficiency .

4-Treatment of cyanide poisoning: IV hydroxycobolamine binds CN- to forms non toxic urinary excreted cyanocobolamine

Preparations :Usually it Vitamin B12 is used IM to bypass slow GIT absorption and intrinsic factor deficiency. Oral preparations are used in combination with desiccated (dried) gastric extract that contain extrinsic factor to promote absorption. IV preparations are used in treatment of cyanide poisoning.

1-Hydroxycobolamine is IV or tablets. It is the only preparation used for treatment of cyanide poisoning.

2-Cyanocobolamine oral and IM .It is cheap

NB: Ethanol increases GIT iron absorption but decrease its utilization it decreases folic acid , vitamin B6 & vitamin 12 absorption. It may cause megaloplastic (Folate or vitamin B12 deficiency) anemia, microcytic anemia due to vitamin B6 deficiency or defective iron utilization.

Drug induced hemolytic anemia

Oxidizing agents that consumes endogenous antioxdants (glutathione) and cause oxidative damage to cell membrane of RBCs

-Paracetamol , sulfonamides , primaquine ,, ascorbic acid , methelene blue, iron , vitamin k .

Autoimmune mediated hemolytic anemia:

Drugs binds to cell membrane of RBCs and change its structure leading to activation of immune system which form anti-RBC cell membrane autoantibodies

Antibiotics , penicillins (pipracellin) , fluoroquinolones (levofluoxacin &nalidexic acid) , nitrofurantoin

Anticancer drugs : fudrapine

Antiinflammatory drugs :NSAIDS (declofenac) , dapsone

Antihypertesive drugs ; alpha methyldopa.

Antiparkinsonian drugs : L-dopa

Antiarrhythmic drugs: quinidine.

Phenazopyridine (pyridium): urinary tract analgesic

Diagnosis of autoimmune hemolytic anemia

Treatment of drug induced hemolytic anemia

Stoppage of causative agent-1

2-Non specific supportive therapy used in any case of hemolytic anemia

In acute hemolysis

-Fresh warm blood transfusion . Cold blood is not used because it may activate cold agglutinins which aggravate hemolysis. Give the lowest possible dose (500-1000 ml)at rate 1ml/kg/hour.

In between attacks

-Iron chelating agents (IV desferoxamine) or Deferasirox, defriprone (low molecular weight) agents to prevent deposition of iron released from hemolysed RBCS. Dferasirox (90 mg tablets) 20 mg /kg once daily and defriprone (100 mg /ml oral solution) 25 mg /kg TDS better than desferoxamine being low molecular weight which allow it to chelate intracellular iron.

-Erythropiotin is a cytokine secreted by the kidney in response to cellular hypoxia it stimulates RBC production in the bone marrow. It is used in hemolytic anemia (sphirocytosis & associated with reticulocytopenia) to decrease requirement for transfusion

-Iron therapy is contraindicated because iron released from hemolysed RBCs is reused except there is low serum iron

Specific treatment of hemolytic anemia

Autoimmune hemolytic anemia

-1st line treatment

1-IV methylprednisolone:500-1000 mg (1/2 -1 vial IV infusion for 3 days followed by oral prednisolone 1-1.5 mg /kg till HB reaches 10g/l

2nd line

1-Ritoximab : monoclonal antibodies against surface protein antigen (CD20) of B lymphocyte. It suppresses B cell mediated immunity. Side effects are increase susceptibility of infection , renal failure due to blockade of renal tubules by proteins released from destroyed B lymphocytes ,acute infusion reaction resulted from infusion of foreign proteins& release cytokines from lysed WBCS causing cardiac arrest , hypotension and tolerance due to formation of antibodies. Dose 1000 mg in 100 ml solvent slowly IV

2-Low dose Immunosuppressive agents : azathioprine (100-150 mg /day), cyclophosphamide(100 mg/day) .They inhibit immune reaction by inhibition of proliferation of lymphocytes.

3-Danazole alone or (200-400 mg /day) in combination with cortiosteroids .

4-IV immunoglobulins (2g/kg) They may interact with pathogenic antibodies or block Fc receptors in macrophages.

5-Exchange transfusion or plasmaphoresis

3rd line

1-High dose cyclophosphamide 50 mg /kg /day for 4days followed by granulcytic colony stimulating factor

2-Alemtuzumab, a humanized monoclonal antibodies against CD52 of lymphocytes (highly toxic)

3-Hemopiotic stem cell transfusion

sickle cell (HBS) anemia

Hydroxyurea which liberate nitric oxide which stimulate production of hemoglobin F which is less toxic and does not precipitate in acidic medium as hemoglobin s which causes sickle crisis.

Other uses:

-Polycythemia, thrombocytosis, leukemia) & malignant tumors because it inhibits ribonucleotide reductase responsible for formation of desoxyribose required for DNA synthesis

Dose :oral 40 mg /kg (2 capsules) TDS reduced by 50% after improvement

Side effects :renal failure , depression of rapidly dividing cells (bone marrow , gonads, skin & mucous membrane).

Complement induced hemolytic anemia:

1- Ecluzimab: complement C5monoclonal antibodies. It blocks autoimmune reaction by blocking complement activation. Dose 600-900 mg (2-3 vials) slow IV infusion

Side effects are similar to ritoximab.

2-Anabolic steroids or danazole (200-400 mg day oral)It induces expression of Complement C1 esterase inhibitor which inhibit complement pathway of immune reaction

Splenectomy

For extra-vascular and autoimmune hemolytic anemia

Drug induced aplastic anemia

I-Dose dependent (delayed onset &predicatable)

A- inhibitors of rapidly dividing cells

- All antineoplastic agents , immunosuppressants and biogenic slow acting disease modifying antiinflammatory drugs , interferon alpha
- Some antimicorbial : chloramphicol , flurocytosine , dapson.
- Colcichine : inhibits mitotic spindles

B-Free radical formation :

Benzene and benzene containing substances: kerosine , carbon tetrachloride , insecticides (parathion , landane) because they are metabolized in the liver to hydroquinones and free radicals which directly stimulate apoptosis and destroy bone marrow stem cells

II-Dose independent ,immune or idiocyncrasy mediated (rapid onset & unpredicatable):

- Antimicrobial :chloramphicol , dapson
- Antiinflamamtory : Indomethacine , penicillamine
- Antiepileptics : carbamazipine , phenytoins, primidone
- Heavy metals : gold , arsenic ,
- Antiarrhythmic : quinidine , procainamide ,tocanamide
- Antithyroid drugs: thiurea , potassium perchlorate
- Antihypertensives : captopril , methyldopa , enalpril
- Antipsychotics : chlorpromazine , prochlorpromazine
- Hypoglycemic agents : Sulfonylurea (chloropamide)

Drug induced agranulocytosis :Granulocytes below 200 cells/mm

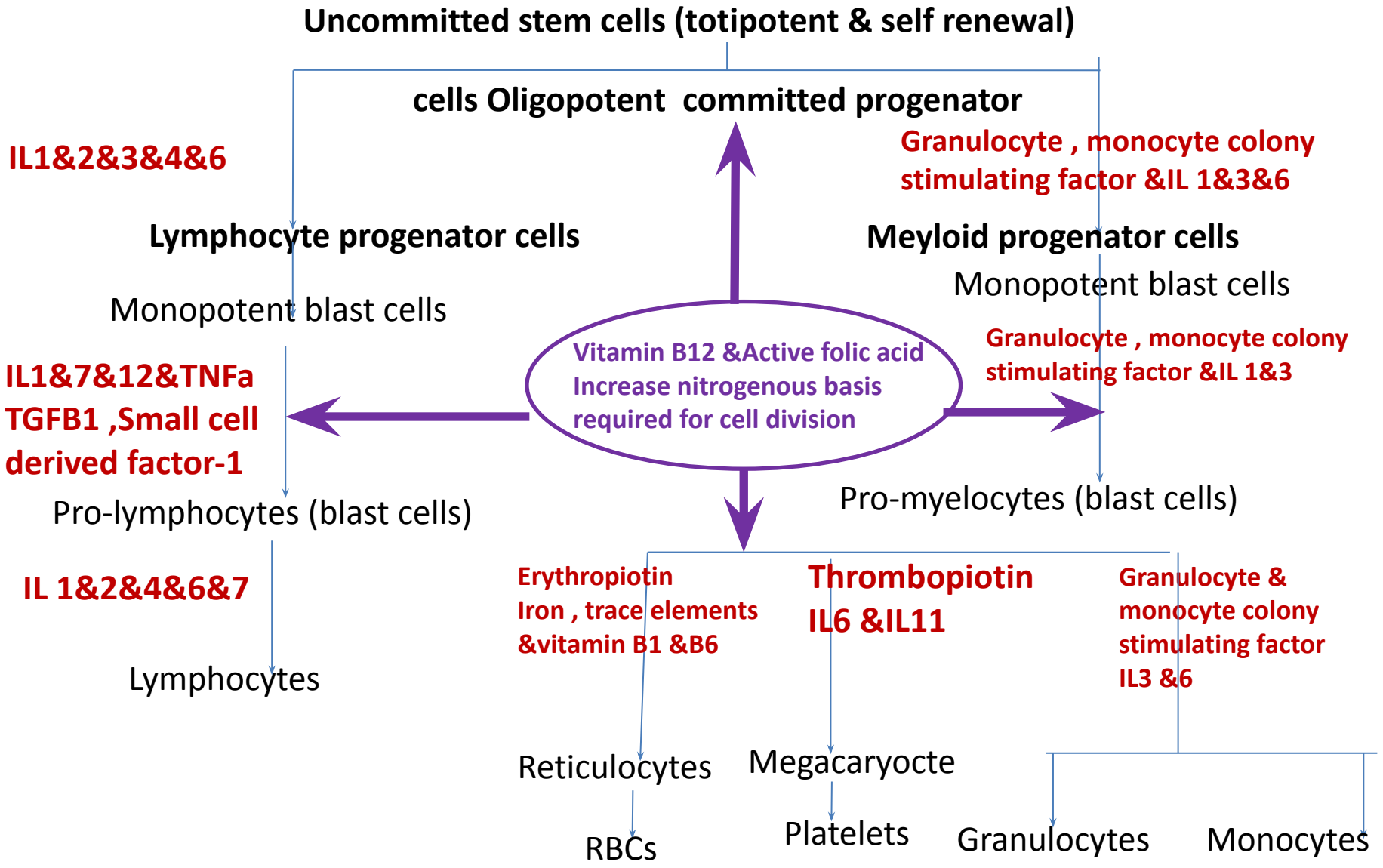
- **Isolated neutropenia**
- **Isolated eosinopenia**
- **Isolated basopenia**

The same drugs that produce aplastic anemia + valproic acid (antiepileptic) ,mianserin , miretzapine ,(antidepressants) , clozapine (antipsychotic) ,benazipril (antihypertensive) , dipyrone , naproxyne (analgesic), allopurinol (antigout) , benzimidazole (antiparasitic) , vancomycin & sulfonamides (antibiotics) , defireprone (iron chelating agent),sulfasalazine , cimetidine , ranetidine (H2 blockers).

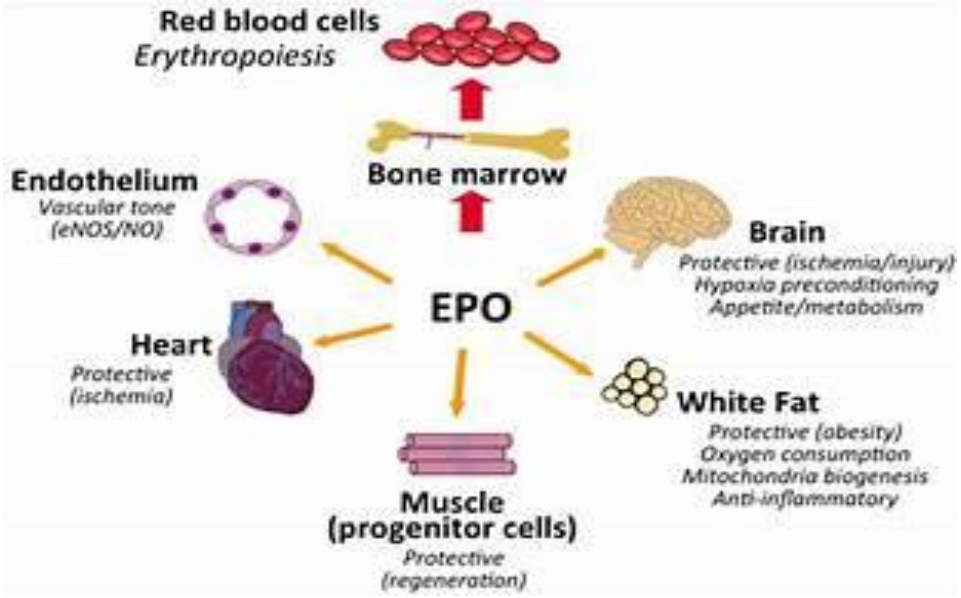
Drug induced thrombocytopenia

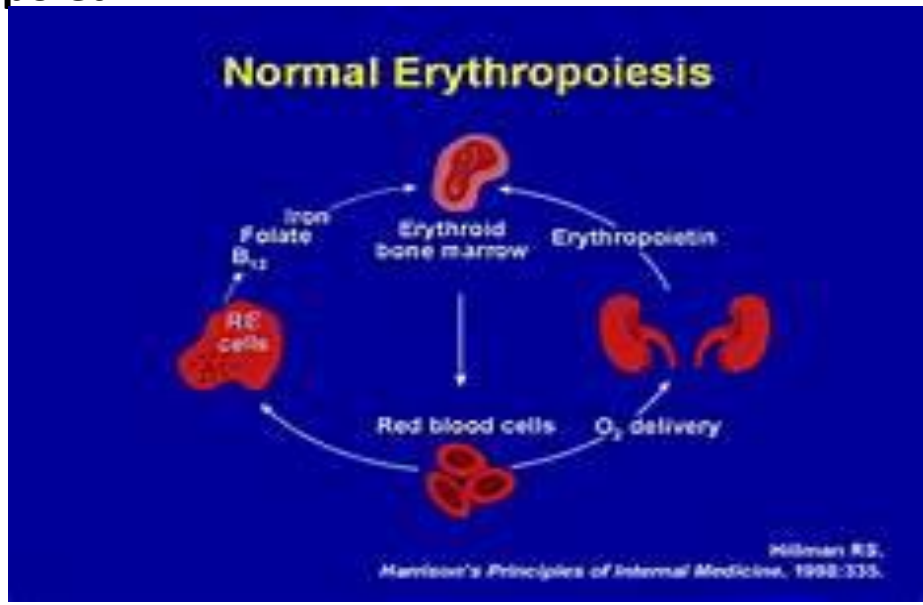
The same drugs that produce agranulocytosis +abciximab , tirofibran (antiplatelet) , danazole , refampicin (antibiotic)

Hematopoisis &Hemopiotic growth factors



RBC specific hematopoietic growth factors
Erythropoietin





: It induces late stages of RBC formation (erythroblast conversion to mature RBCS)

It is used in cases of

-Aplastic anemia

-Hemolytic anemia to reduce exogenous blood transfusion

-Anemia due to renal failure to replace renal secretion of endogenous erythropoietin

-In doping to increase physical fitness of athletes

-Autologous blood transfusion: before surgical operations .

Side effects :-Immune reaction caused by injection of foreign protein :flu like symptoms , skin rash, itching

-Headache , hypertension ,thrombosis due to increase blood viscosity as a result of excessive RBC production

-Sternal bone pain due to bone marrow expansion.

-Iron deficiency anemia as a result of excessive RBC formation.

-Antibody formation leading to tolerance (pure red cell aplasia).

Preparations :

- Recombinant Short acting preparations :Erythropoietin (epeotin a) is injected sc or IV 3 times / week
- Long acting preparations :pegylated epeotin B & polyglycosylated erythropioin(darbipeotin): once /1-4 weeks

Platelet specific hematopoietic growth factors

1-Thrombopiotin receptor agonist

(Romiplostine) : synthetic protein analogue of thrombopoietin (platelet activating hormone)

-It stimulates differentiation of megakaryocytes to platelet through JANUS /mitogen activated protein kinase pathway.

-It is used in treatment of thrombocytopenia

-It is injected SC 1ug/kg /week until platelet Count is over 50,000 then reduce the dose Gradually and stop drug if platelet count is Over 150,000 /mm

-Side effects :- Thrombocytosis , thrombosis

-Bone marrow fibrosis due to increase collagen and reticulin formation in bone marrow by activation of I3K pathway of cell division , anemia ,

-Ischemia , myalgia

2-Oprevakin: recombinant IL11.

-It stimulates differentiation of megakaryocytes to mature platelets , healing of endothelium and intestinal epithelium , inhibition of adepogenesis

-It is used in treatment of chronic thrombocytopenia due to chemotherapy , liver cirrhosis or malignancy

-Dose is 25–50 µg/kg per day sc 1day before chemotherapy and discontinued 2 days before next cycle of chemotherapy. It is stopped if platelet count reach 50000/mm

Side effects:-Allergic reaction , itching , bronchospasm , hypotension

-Fluid retention duo to:

1- Direct effect of drugs on sodium reabsorption from renal tubules

2-Capillary leak syndrome (differentiation syndrome) resulting from release of cytokin from proliferative myelocytes.This leads to:

- Hyertension , headache , systemic and pulmonary edema heart failure .
- Blurring of vision ,optic disc edema
- Atrial arrythmia due to sodium retention and increase blood volume.

-Increase cortical bone thickness due to stimulation of osteogenesis

-Teratogenic

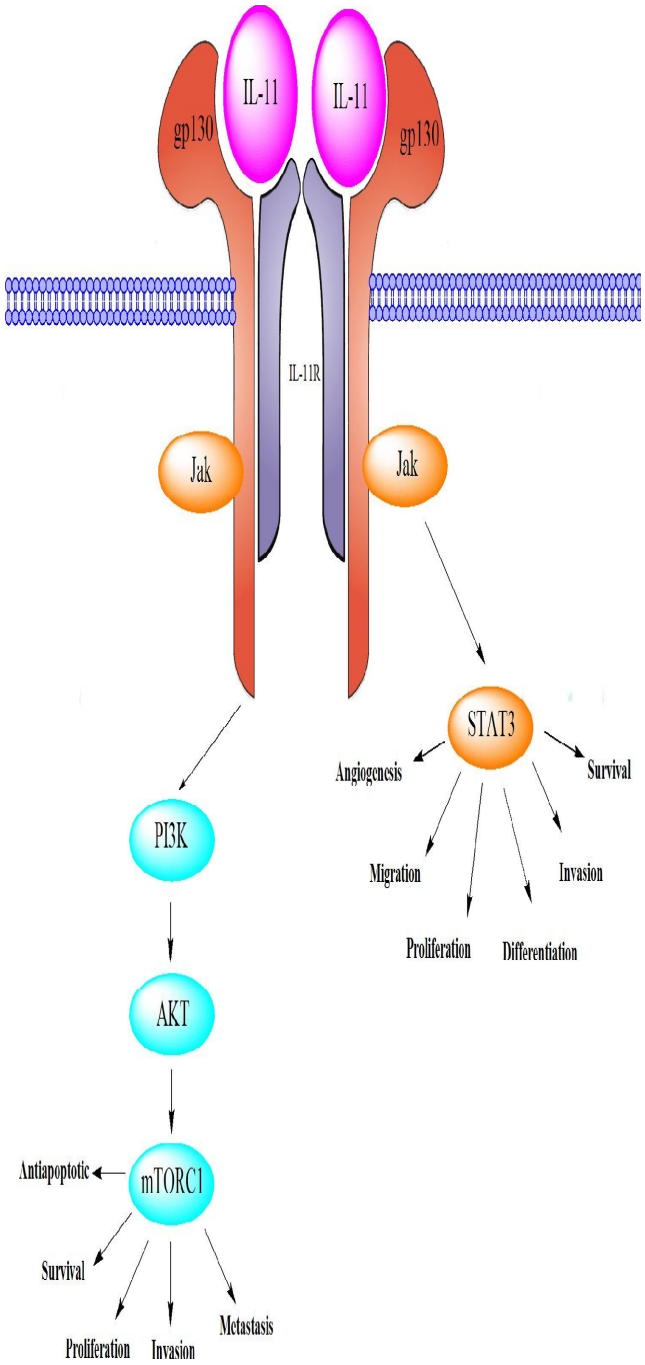
Eltrombopag-3

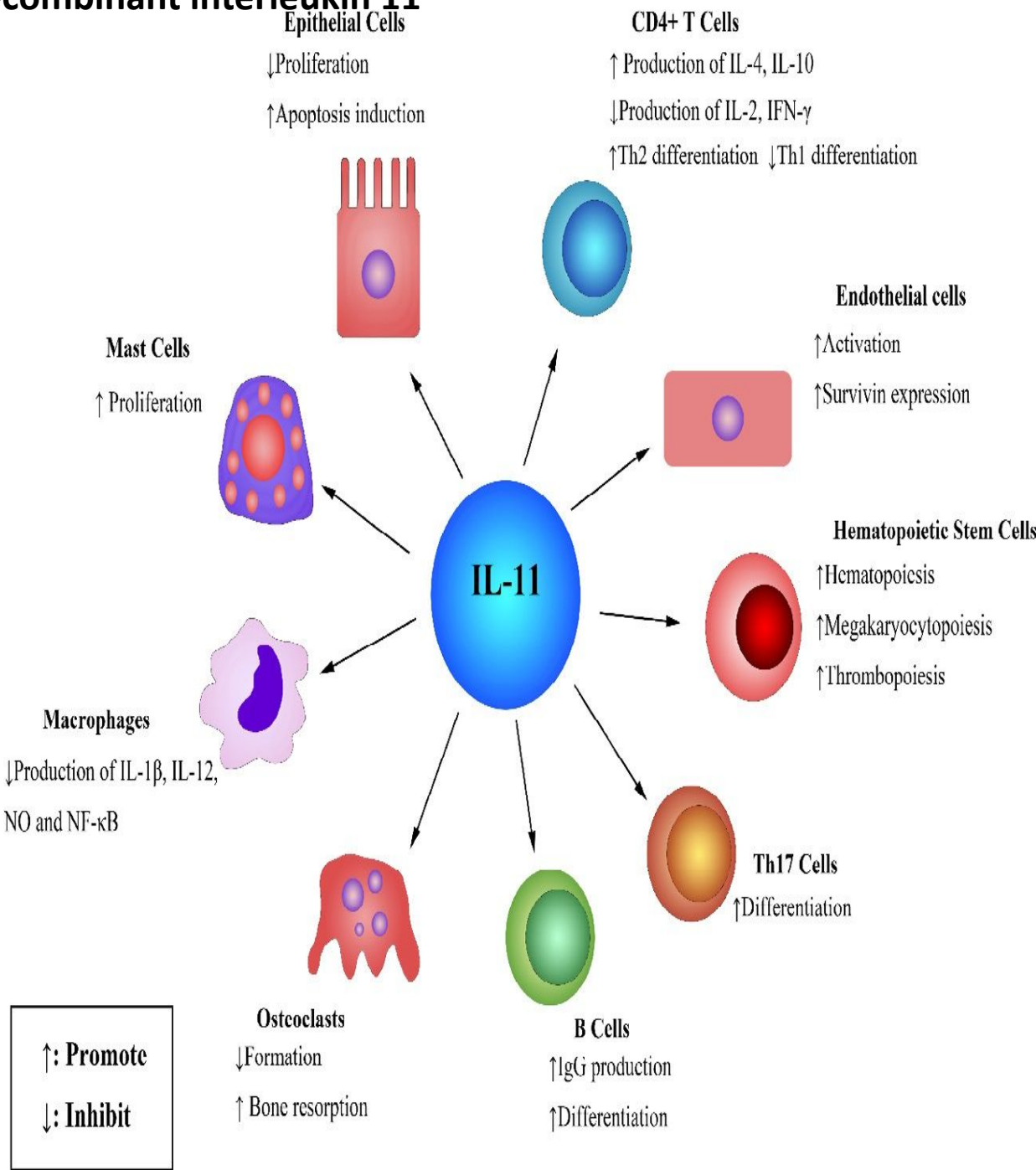
-Orally active small molecular weight thrombopoietin receptor agonist. It stimulates STAT but not Akt pathway. It does not cause fluid retention. Side effects are GIT upset , allergic reactions , flu like symptoms , myaligia , sore throat , .

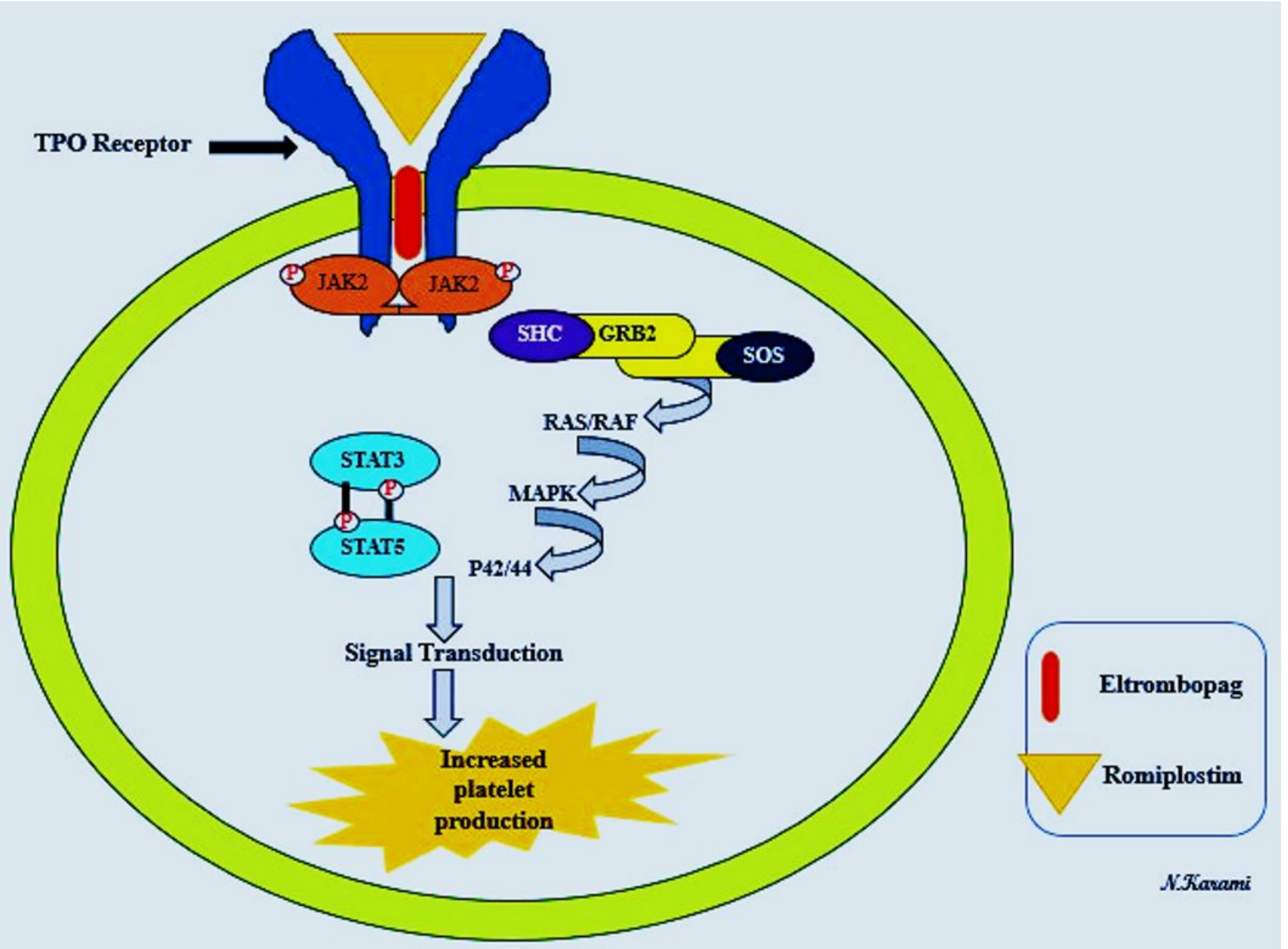
-Dose is one tablet (50 mg) 4 times daily

NB; thrombopoietin is not used clinically due to rapid development of tolerance.

Oprevakin (recombinant interleukin 11






TPO Receptor
JAK2
JAK2
SHC
GRB2
SOS
RAS/RAF
MAPK
P42/44
STAT3
STAT5
Signal Transduction
Increased platelet production
Eltrombopag
Romiplostim
N.Karami

GRANULOCYTE specific hematopoietic growth factors

Recombinant granulocyte colony stimulating factor. It is used for treatment of

- Chemotherapy induced agranulocytosis. They are commonly used in acute myeloid leukemia. The drugs are administrated 4days after completion of chemotherapy cycle and continued till neutrophils becomes more than 500/mm3 . They are not used 1 day prior or after chemotherapy
- Prior to stem cell transplantation in order to increase peripheral stem cells
- Radiation induced and idiopathic agranulocytosis.The drugs are given as early as possible .
- To stimulate bone marrow after bone marrow transplantation.The drugs are administrated immediately after bone marrow transplantation.
- Aplastic anemia

-**Side effects**:

- Bone pain
- Local pain at the site of injection
- Allergic reaction : itching ,edema , hypotension probably mediated by drug solvents
- Rupture spleen
- Bleeding (hemoptosis , alveolar hemorrhage).
- Precipitation of sickle crisis in patients with sickle cell anemia

Preparations

Short acting preparation:

1-Filgrastim (300 mcg vial)is administered by subcutaneous injection or intravenous infusion over at least 30 min at doses of 1–20 μg/kg/d once /day .

2-Sargramostim (500 mcg / ml vial) : 250 mcg /m2 over 4 hours or subcutaneous 4 times daily

Long acting : -Pigylated filgrastim 6 mg sc once /chemotherapy cycle

Treatment of anemia due to bone marrow failure

Aplastic anemia: defect formation of all blood cells

1-Non specific general measures

-Blood transfusion in severe acute cases

-Bone marrow stimulants in chronic cases:

*Oral corticosteroids 1-2 mg/kg /day

*Anabolic steroids derived from male sex hormones :Nandrolone decanuate :50 mg IM /month.

*lithium carbonate: 300 mg (one tablet TDS)

Autoimmune aplastic anemia due to autoimmune destruction of bone marrow cells by overactive lymphocytes is treated by

*Antilymphocytic globulins: rabbit or mouse derived antibodies against human lymphocytes.

*Balilximab &Decluzumab: monoclonal antibodies against IL2 receptors on the surface of T lymphocytes .They act by blockade of natural proliferation of lymphocytes induced by interleukin

-They are also used in treatment of organ rejection

-Side effects are similar to ritoximab

Other types of Aplastic anemia caused by drugs (anticancer or antiviral drugs) ,irradiation cancer therapy cancer or premature babies are treated by:

*General measures:

*Erythropiotin to stimulate RBC production

*Recombinant granulocyte colony stimulating factor to increase WBCS

*Thrombopiotin receptor agonists :Romiplosin to increase platelets

Selective decrease of specific blood cells

Selective decrease in RBCS caused by impaired erythropiotin Production in chronic renal failure

Treatment: recombinant Erythropiotin (epeotin) is injected sc or IV 3 times / week for Short acting preparations epeotin α once / 1-4 weeks for month for long acting preparations polyglycosylated erythopiotin (darbipeotin) or pigylated(combined with ethelene glycol) epeotin β

-Other uses:-To stimulate bone marrow in cases of autogenic blood transfusion and athletes to increase physical fitness (doping).

-Side effects :-Immune reaction caused by injection of foreign protein :flu like symptoms , skin rash, itching

-Headache , hypertension ,thrombosis due to increase blood viscosity as a result of excessive RBC production

-Sternal bone pain due to bone marrow expansion.

-Iron deficiency anemia as a result of excessive RBC formation

-Antibody formation leading to Tolerance (pure red cell aplasia)

Agranulocytosis : selective deficiency of WBC below 500/mm3

Treatment: -General measures : blood transfusion is less effective due to short life of WBCS & bone marrow stimulants &avoid infections .

-Non immunosuppressive antibiotics : penicillins

-Recombinant granulocyte colony stimulating factor

- Short acting :(filgramostim or sargramostim
- Long acting piglylated filgrsmin:100 ug sc ,IM ,IV /4 days

Thrombocytopenia is treated by :packed platelet transfusion

-Corticosteroids: prednisolone 1-2 mg /day orally

Thrombopiotin agonists: Romiplostin , orally. Human recombinant thrombopiotin is ineffective due rapid development of tolerance

BLOOD TRANSFUSION

:Indications

1-Replacement transfusion (Replacement of whole or specific blood constituents)

- To replace whole blood in cases of hemorrhage.
- To replace red blood cells in cases of severe anemia (HB below 8 g/dl) whole or packed RBCS are used
- To replace platelets in cases of thrombocytopenia .Packed platelets are used
- To replace fibrinogen and clotting factors in cases of hemorrhagic blood diseases .

2-Exchange transfusion : In cases of autoimmune diseases to remove harmful constituents (autoantibodies) in patients blood by removing blood of patient and replace it with normal donor blood.

3-Doping transfusions : Athletes & military personells undergo blood transfusion to increase their physical capacity before sporting events ,dilute and prevent detection of forbidden drugs in their blood.

Sources of blood transfusion

- Autologous :The patient receives his own blood pre-donated before surgery or collected during surgery by special device
- Allogeneic (homologous) :Patient receives blood of other person(donor).Persons with O blood group is the most preferable because they can donate their blood to any persons in small amounts because their RBCS contain no A or B antigens

Storage of blood

Blood withdrawn from donor is stored at 4 ^{0}C with anticoagulant (3.8%sodium citrate solution) and glucose to provide optimal nutrition to red blood cells. It is expired after 42 days of storage.

- Fresh blood : Blood stored for less than 4 days .It provide coagulation factors .
- Old blood :Stored for 4 -42 days .It does not provide coagulation factors
- Leukoreduced blood: Most of leukocytes are removed from transfused blood by filtration to prevent transmission of intracellular harmful microorganisms (TB , virus) and avoid suppression of immune cells of recipient by donors leukocytes
- Packed blood constituents: Packed RBCS and packed platelets are used in anemia and thrombocytopenia to provide required blood constituents and prevent over transfusion

Complications of blood transfusion

1-Hemolytic reaction : Released free hemoglobin from hemolysed RBCS is precipitated as insoluble acid hematin in acidic media of renal tubules leading to acute renal failure manifested as fever , chills , hematuria and anuria (marked decrease in urine formation below 500 ml /day). It occurs due to:

- Acute hemolytic reaction occurs within 24 hours of transfusion due to ABO incompatibility or use of expired blood.
- Delayed hemolytic reaction occurs after more than 24 hours of transfusion due to RH incompatibility
- Treatment:-Stop transfusion immediately

-Give alkaline salts (sodium bicarbonate or 1/6 molar sodium lactate) to alkalinize urine.
-Give osmotic diuretic (mannitol IV drip) to prevent anuria.

2-Pyrogenic reaction :It is due to the presence of pyrogens (antigens from dead bacteria) in the apparatus used for blood transfusion. This causes fever and chills. It is treated by- IV hydrocortison semisuuccinate 100 mg IV,10 ml of 10%Calcium gluconate slowly IV drip + H1 blockers (diphenhydramine 50 mg) intramuscular.

3-Immunological reactions : due to presence of antibodies in donors blood that react with recipient cells

Acute reactions

-Anaphylactic shock mediated by donors IgA
-Allergic skin rash and rhinitis mediated by donors IgE
-Acute respiratory distress syndrome mediated by antibodies against recipient human leukocytic antigen

Delayed reaction

-If recipient is immunosuppressed donors T lymphocytes attacks recipient cells causing diarrhea, hypotension , fever
-On repeated transfusion : recipient produces antibodies against donor s platelets leading to hemorrhage

4-Overtransfusion cause heart failure and pulmonary edema treated by Loop diuretics (furosimide IV& amionophylline IV and +ve inotropic drugs (dopamine or doputamine), morphine 5 mg slow IV to reduce pain and anxiety

5-Repeated transfusion causes

- Post-transfusion thrombocytopenia because recipient produces antibodies against donor s platelets.
- Hemosiderosis skin pigmentation with hemosidren(iron pigment) treated by chelating iron with desfexamine.

5- Massive transfusion: causes hypothermia , hyperkalemia (release of potassium from transfused hemolysed RBCS, bleeding due to dilution of clotting factors , hypocalcemia due to precipitation of calcium by citrate in transfused blood

6-Transfusion of infections (AIDS &Hepatitis C & from donor to recipient. Pre-exposure to ultraviolet rays reduce infection.

7-Faulty technique causes air embolism which causes acute circulatory failure.

Adjustment of volume of transfused blood

- In emergency conditions start with 500 ml (one unit) of saline + one unit of blood +one unit of packed RBCS then adjust dose according to severity of shock and response of patient
- Volume of transfused blood in non emergency conditions $= \frac{Weight\ (KG) * deficient\ HB\ concentration\ (g/L) * 3}{Hematocrit\ value}$ or 10 ml /kg

Plasma transfusion

Types of whole plasma

1-Liquid plasma : Separated from blood by centrifugation .It is stored in concentration of 5% in 50% glucose solution at 4 ^{0}C.

2-Dried plasma: separated from liquid plasma by lyophilization (dry freezing) . It is stored dried in 4^{0}C and dissolved before use in half normal saline +2.5 % glucose. The dose is 10 ml /kg

3-Fresh Frozen plasma: prepared by freezing fresh liquid plasma at -15^{0}C. It is the only plasma preparation that preserve clotting factors .It is solubilized in warm water bath and administrated in a dose of 10-20 ml/kg IV in hemorrhagic diseases

4-Synthetic plasma: solution containing the same ion concentration of human plasma used in gene therapy & fixation of bone metal implants

Indications

I-Replacement therapy

1-The first line treatment of burns

2-As an alternative for whole blood transfusion if not available .It keeps osmotic pressure but has very little oxygen carriage

Advantages : It is storage for long times (months or years)

-It keeps osmotic pressure of blood and retain in circulation for long time

-It does not need cross matching if transfused in small amounts.

-Immunological and febrile reactions are rare

Disadvantages :-They have very limited oxygen carrying capacity

-It may transmit infections

-Overdose may cause heart failure

II-Exchange therapy(plasmaphoresis): Removal of patient plasma which contain harmful autoimmune antibodies and replacing it normal plasma. It is two types:

Autologous: patient plasma is withdrawn , treated and re-injected

Homologous patient plasma is withdrawn and replaced by donor one.

Plasma constituents

1-Human serum albumen is used to

1-As blood or plasma substitute in hypovolemic shock

2-In cases of hypoalbumemia as a result of

- Decrease synthesis in malnutrition ,starvation , mal-absorption or liver diseases
- Excessive loss in urine in nephrotic syndrome
- Excessive loss by skin in burns
- Severe abdominal inflammation eg peritonitis , pancreatitis

Dose : 500 ml of 5% or 200 ml of 25 % solution slowly by IV drip.

2-Human gamma globulins : They protect against infectious diseases by provision of antibodies .They have two types:

Immunoglobulins :It contains non committed antibodies .

Hyperimmune gamma globulins : it is prepared from the plasma of donors with high titers of antibodies against a specific organism. Hepatitis B , tetanus toxin, herpes zoster, hepatitis A, or cytomegalovirus They are used to prevent infections in susceptible persons or during epidemics.

Human fibrinogen :It is used in bleeding disorders eg hypofibrinogenemia and disseminated intravascular thrombosis.

Human factor VIII is used for hemophila

Fibrin glue :consists of fibrinogen + bovine thrombin .It is used in lacerated wounds