Blood Pharmacology 2

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Objectives

1. Understand the role of Haematinics: Iron, Folic acid and Vitamin B12
2. Describe the use of Haemopoietic growth factors: Erythropoietin Stimulating Agents, Granulocyte-Colony Stimulating Factors and Granulocyte-Macrophage Colony Stimulating Factors, and Interleukin 11
3. Understand the rationale of Drug therapy for reducing sickling crises in sickle cell disease
4. Describe the use Drug therapy for sideroblastic anaemia

IRON

Iron

An essential mineral found in hemoglobin, myoglobin, and many enzymes.

Absorbed in acidic duodenum by active transport. Enters the bloodstream and transported to organs of the reticuloendothelial system **(liver, spleen, bone marrow)** where it is and becomes part of iron stores.

Therapeutic Effect(s): Resolution of iron deficiency anemia.

Absorption: Approximately 5–10% of dietary iron is absorbed (up to 30% in deficiency states). Absorption with IV administration is complete. Well absorbed following IM administration.

Distribution: Remains in the body for many months. Crosses the placenta; enters breast milk.

Protein Binding: ≥90%.

Metabolism and Excretion: Mostly recycled; small daily losses occurring via desquamation, sweat, urine, and bile.

Contraindications

- Anaemia not due to iron deficiency
- Hemochromatosis
- Hemosiderosis
- Hypersensitivity to iron dextran

Use Cautiously in:

- Severe hepatic impairment
- Pre-existing cardiovascular disease (disease may be exacerbated by adverse reactions to iron dextran)
- Significant allergies or asthma
- History of drug allergy or multiple drug allergies (may be at ↑ risk for anaphylactic reaction)
- Rheumatoid arthritis (may have exacerbation of joint swelling)
- OB: Lactation: Pregnancy or lactation.

Adverse Reactions/Side Effects

CNS: SEIZURES

CV: hypotension, **GI:** abdominal pain, nausea, vomiting, taste disorder

Derm: flushing, urticaria

Local: pain at IM site, phlebitis at IV site, skin staining at IM site

MS: arthralgia, myalgia

Misc: ALLERGIC REACTIONS INCLUDING ANAPHYLAXIS, fever, lymphadenopathy, sweating

Lab Test Considerations

Monitor hemoglobin, hematocrit, and reticulocyte values prior to and every 3 wk during the first 2 mo of therapy

Monitor hemoglobin, hematocrit, reticulocyte values, transferrin, ferritin, total iron-binding capacity, and plasma iron concentrations periodically during therapy.

Toxicity Overdose

Early symptoms of overdose: stomach pain, fever, nausea, vomiting (may contain blood), and diarrhea.

Late symptoms: bluish lips and palms; drowsiness; weakness; tachycardia; seizures; metabolic acidosis; hepatic injury; and cardiovascular collapse.

Hospitalization continues for 24 hr after patient becomes asymptomatic to monitor for delayed onset of shock or GI bleeding.

Late complications: intestinal obstruction, pyloric stenosis, and gastric scarring.

If patient is comatose or seizing, gastric lavage with sodium bicarbonate is performed.

- Deferoxamine is the antidote.
- supportive treatments to maintain fluid and electrolyte balance and correction of metabolic acidosis

FOLIC ACID

Folic Acid Indication

Prevention and treatment of megaloblastic and macrocytic anemias.

Given during pregnancy to promote normal fetal development.

Stimulates the production of red blood cells, white blood cells, and platelets. Necessary for normal fetal development.

Therapeutic Effects: Restoration and maintenance of normal hematopoiesis by Increased synthesis of tetrahydrofolate.

Folic Acid Pharmacokinetics

Absorption: **Well absorbed** from the GI tract and IM and subcutaneous sites.

Distribution:

- Half of all stores are in the liver.
- Enters breast milk. Crosses the placenta.

Protein Binding: Extensive.

Metabolism and Excretion: Converted by the liver to its active metabolite, **dihydrofolate reductase**.

Excess amounts are excreted unchanged by the kidneys.

Contraindications and Side effects

Contraindications: Uncorrected pernicious, aplastic, or normocytic anemias (neurologic damage will progress despite correction of hematologic abnormalities);

Use Cautiously in: Undiagnosed anemias.

Side Effects:		
Derm: rash	CNS: irritability, difficulty sleeping, malaise, confusion	Misc: fever

Drug Interactions

Pyrimethamine, methotrexate, trimetho prim, and triamterene prevent the activation of folic acid

leucovorin should be used instead to treat overdoses of these drugs.

Reduced absorption of folic acid by sulfonamides (including sulfasalazine), antacids, and cholestyramine .

Folic acid requirements are increased with estrogens, phenytoin, phenobarbital, primidone, carbamazepine, or corticosteroids .

Folic acid may lower phenytoin levels.

Vitamin B12/ Cobalamin

Vitamin B12

Indication: corrects **pernicious anaemia.**

Dietary sources are meat (**particularly liver, where it is stored**), eggs and dairy products.

Absorption requires **intrinsic factor** (a glycoprotein secreted by gastric parietal cells).

- Vitamin B12-intrinsic factor complex is absorbed by active transport in the terminal ileum.

Patients with pernicious anaemia (an autoimmune disorder where **lining of the stomach atrophies). Other risks:**

- Total gastrectomy
- Surgical removal of the terminal ileum also impairs B12 absorption.

Vitamin B12

If vitamin B12 absorption stops suddenly , it takes 2– 4 years for evidence of deficiency to manifest.

Hydroxocobalamin is given by injection4 because vitamin B12 deficiency commonly results from malabsorption.

Patients with pernicious anaemia require life-long therapy, with maintenance injections every 3 months following a loading dose.

Vitamin B12 and folic acid

Both vitamin B12 and folic acid are needed for DNA synthesis.

Deficiencies affect erythropoiesis, causing macrocytic megaloblastic anaemia and hypersegmented neutrophils.

There is active uptake of folic acid into cells and reduction to tetrahydrofolate (FH4) by dihydrofolate reductase

Folate polyglutamate is a co-factor synthesis of purines and pyrimidines (especially thymidylate).

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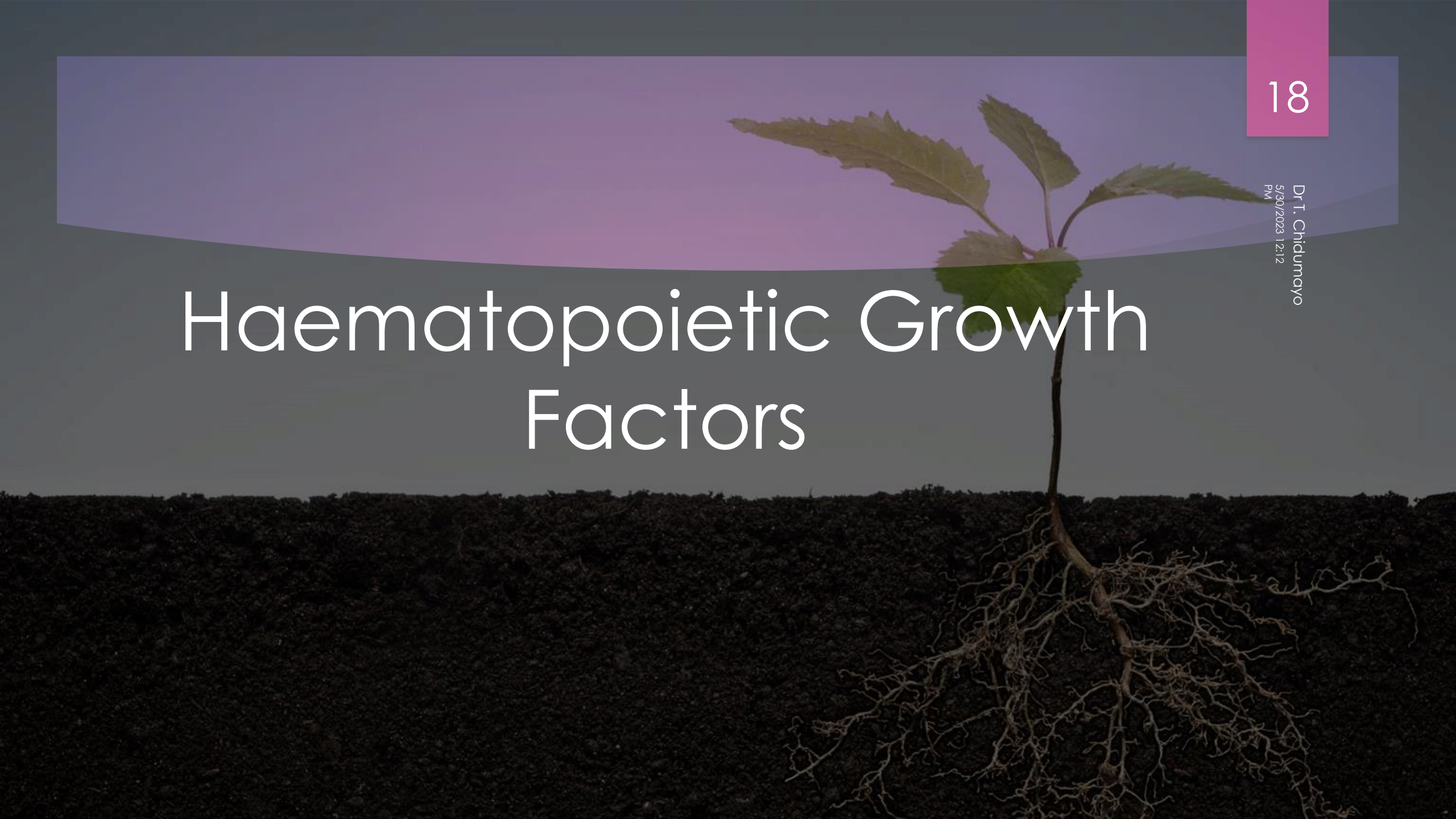
Haematopoietic Growth Factors



Haematopoietic Growth Factors

The body produces 120 million granulocytes and 150 million erythrocytes, numerous mononuclear cells and platelets, per minute.

Maintenance of haematopoiesis necessitates a balance between self-renewal of the stem cells and differentiation into the various types of blood cell .

Haematopoietic growth factors direct the division and maturation of the progeny of these cells down eight possible lines of development.

Cytokine growth factors are present in plasma at very low concentrations under basal conditions.

Concentrations increases by 1000-fold or more within hours after stimulation.

Clinical Uses of Colony-Stimulating Factors

Iron or folate deficiency must be corrected before starting treatment.

Colony-Stimulating Factors CSFs are cytokines that stimulate the formation of maturing colonies of leukocytes, observable in tissue culture.

They stimulate particular committed progenitor cells to proliferate and cause irreversible differentiation.

The responding precursor cells have membrane receptors for specific CSFs and may express receptors for more than one factor.

Haematopoietic growth factors Erythropoietin

- Regulates red cell production
- Given intravenously, subcutaneously, intraperitoneally
- Can cause transient flu-like symptoms, hypertension, iron deficiency and increased blood viscosity
- Available, as epoietin, to treat patients with anaemia caused by chronic renal failure

Clinical uses of epoietin

Anaemia of chronic renal failure

Anaemia during chemotherapy for cancer

Prevention of the anaemia that occurs in premature infants (unpreserved formulations)

- Preservative associated with a fatal toxic syndrome in neonates

To increase the yield of autologous blood before blood donation

Anaemia of AIDS (exacerbated by zidovudine).

Granulocyte CSF

Granulocyte CSF is produced mainly by monocytes, fibroblasts and endothelial cells.

- Controls the development of neutrophils
- Increase proliferation and maturation
- Stimulate their release from bone marrow storage pools
- Enhancing their function.

Recombinant forms: **Unglycosylated filgrastim** and **glycosylated lenograstim** are used therapeutically.

Pegfilgrastim is a pegylated filgrastim derivative with increased duration of action.

Given parenterally for Stimulates neutrophil progenitors.

Clinical uses of the colony-stimulating factors

- Used in specialist centres to reduce severity/ duration of neutropenia induced by cytotoxic drugs during:
  - Intensive chemotherapy necessitating autologous bone marrow rescue
    - After bone marrow transplant.
    - Harvest progenitor cells.
    - To expand the number of harvested progenitor cells ex vivo before reinfusing them.
    - For persistent neutropenia in advanced HIV infection.
    - In aplastic anaemia.

Unwanted effects Erythropoeitin

Transient influenza-like symptoms

Hypertension is also common and can cause encephalopathy with headache, disorientation and sometimes convulsions.

Iron deficiency can be induced because more iron is required for the enhanced erythropoiesis.

Blood viscosity increases as the haematocrit, **increasing the risk of thrombosis,** especially during dialysis.

PURE RED CELL APLASIA (PRCA) caused by neutralising antibodies directed against erythropoietin

- **Inactivates the endogenous hormone as well as the recombinant product**

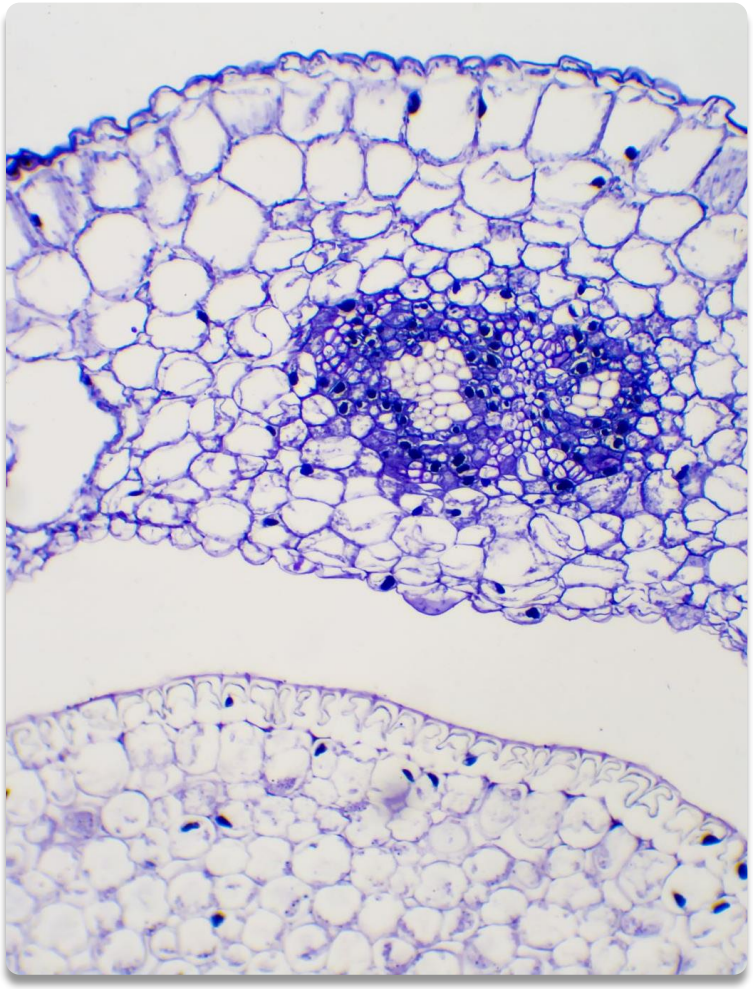
Immunogenicity is unpredictable and can be caused by seemingly minor changes in manufacture or storage.

Interleukin 11/ IL11/Neumega, oprelvekin, and rhIL-11 AGIF

Interleukin 11 is a Cytokine that:

- Stimulates T-cell-dependent development of immunoglobulin-producing B cells.
- Support the proliferation of hematopoietic stem cells.
- Support the proliferation **megakaryocyte** progenitor cells.

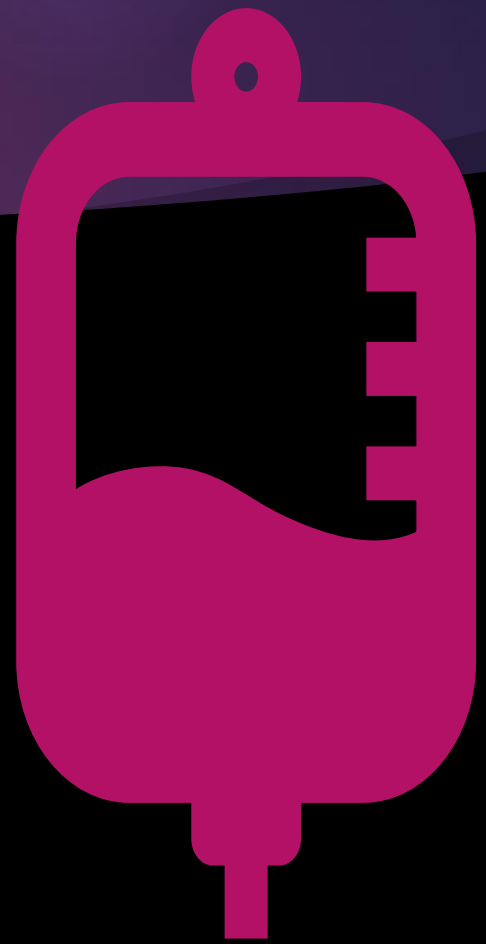
Oprelvekin, the recombinant form of interleukin-11, is used in treatment of severe thrombocytopenia due to chemotherapy for non-myeloid malignancies. .



Sickle Cell Disease

Sickle Cell Disease

- Hereditary, hemoglobinopathy marked by chronic hemolytic anemia, acute episodes of painful “crises,” and increased susceptibility to infections
- The heterozygous condition (Hb AS), sickle cell trait, is usually asymptomatic without anemia.
- **General Measures:**
- Painful crises: hydration, analgesics; oxygen regardless of whether the patient is hypoxic
- Influenza vaccine yearly
- Conjugated pneumococcal vaccine
- Meningococcal vaccine



Reducing sickling crises in sickle cell disease

Hydroxyurea for prevention of painful acute chest syndrome, vaso-occlusive episodes, and very severe anaemia.

- Increases fatal haemoglobin concentration.
- Monitor blood counts (avoid severe neutropenia, thrombocytopenia)

Precautions:

- Avoid high-dose oestrogen oral contraceptives; consider Depo-Provera.
- G-CSF use is contraindicated as it may lead to vaso-occlusive episodes and multiorgan failure.

Second Line: Folic acid

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Sideroblastic anaemia

Sideroblastic anaemia

Sideroblastic anaemia is a type of anaemia that results from **abnormal utilization of iron during erythropoiesis**.

Marked by presence of **ring sideroblasts** in the bone marrow.

- Ring sideroblasts are erythroid precursors containing deposits of non-heme iron in mitochondria forming a ring-like distribution around the nucleus.
- Sideroblastic anaemia may cause microcytic and macrocytic anaemia depending on type of mutation involved.
- Patients have normal to high iron levels.

Management of sideroblastic anaemia

- Depends on severity.
- Patients with a mild or asymptomatic presentation: follow up in the outpatient clinic.
- Patients with the X-linked sideroblastic anaemia:
  - oral pyridoxine 50-100mg/day
  - Blood transfusion in unresponsive patients with severe anaemia.
- For patients who require chronic transfusion:
  - Iron chelation to avoid iron overload with deferoxamine or oral chelators
  - Iron overload could result in unresponsiveness of pyridoxine.
  - Patients with normal haemoglobin levels after pyridoxine should get phlebotomy as a treatment for iron overload.

Management of sideroblastic anaemia cont.

Secondary acquired sideroblastic anaemia may be caused by drugs or toxins:

Discontinue and avoided the drugs.

Anaemia will improve after the removal of the drug.

Copper should be replaced in a patient with copper deficiency via nutrition.

For patients with MDS/MPN-RS-T, aspirin therapy is recommended if the patient has additional JAK2V617F mutation.

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Clinical Scenario 1

- An elderly patient with anaemia three years after a gastrectomy necessitated by a chronic peptic ulcer. She presents with anaemia despite having monthly cobalamin injections. Her **red blood cell count 2.8 × 106/ mm3** (normal, female 3.5 – 5.5 × 106/ mm3), **mean corpuscular volume 60 fL (normal 80 – 100 fL**), **haemoglobin 8.6 g/ dL** (normal, female > 12g/ dL), **haematocrit 32% (normal 36 – 46%).** Which of the following drugs given orally would most likely improve the patient's condition?

A. A. Vitamin B12
B. B. Folic acid
C. C. Iron dextran
D. D. Erythropoietin
E. F. Ferrous sulfate

Facts about Iron

Gastric acid is necessary to convert dietary iron to a form that is readily absorbed by the duodenum.

Iron deficiency anemia does not occur for a few years after gastrectomy

- iron is stored in moderately large amounts in bone marrow.

When mild anemia is caused by iron deficiency, oral iron supplementation is appropriate.

Clinical Scenario 2

The blood results of an adult male patient show red blood cell count 3.0 × 106/ mm3 (normal 4.3 − 5.9 × 106/ mm3), mean corpuscular volume 115 fL (normal 80 − 100 fL), vitamin B12 is 90 pg/ mL (normal > 280 pg/ mL), serum ferritin 250 ng/ mL (normal 30 − 300 ng/ mL). What is your diagnosis and most appropriate frug for this patient?

- A. Megaloblastic anaemia/ Folic acid
- B. Microcytic anaemia/ Ferrous sulphate
- C. Iron poisoning/ Deferoxamine
- D. Microcytic anaemia/ Iron dextran
- E. Pernicious anaemia / Cyanocobalamin

Facts about cyanocobalamin

Parietal cells may diminish resulting in reduced intrinsic factor.

Vitamin B12 can not be absorbed without complexing with vitamin B12.

Parenteral cyanocobalamin should be given daily to replenish tissue stores, and a monthly maintenance dose should be given for life.

Clinical Scenario 3

Patients who complete chemotherapy may have autologous bone marrow transplantation. Which drugs may be used after transplantation to expedite neutrophil recovery?

- A. Leucovorin
- B. Filgrastim
- C. Oprelvekin
- D. Cyanocobalamin

Facts about granulocyte colony-stimulating factor

Myeloid growth factor that can stimulate proliferation and differentiation of neutrophil progenitor cells only.

Filgrastim is a human granulocyte colony-stimulating factor that stimulates the production of granulocyte progenitor cells.

Clinical Scenario 4

A patient with anaemia with red blood cell count 3.5 × 106/ mm3 (normal 4.3 − 5.9 × 106/ mm3), mean corpuscular volume 94 fL (normal 80 − 100 fL), haemoglobin 7 g/ dL (normal, male > 13.5 g/ dL), serum iron 42 µg/ dL (normal 50 − 150 µg/ dL), serum creatinine 5.0 mg/ dL (normal 0.6– 1.2 mg/ dL). Which of the following pairs of drugs would be most appropriate to treat the patient's disease?

A. Erythropoietin and ferrous sulfate

B. Erythropoietin and filgrastim

C. Folic acid and oprelvekin

D. Folic acid and iron dextran

Facts about hypoproliferative anaemia

The patient's lab results indicate that he was most likely suffering from a hypoproliferative anaemia due to CKD.

When anaemia is due to renal disease, erythropoietin is the treatment of choice.

Iron supplements must also be given to achieve an adequate erythropoietin response.

Clinical Scenario 4

An 8-year-old sickle cell disease patient with a history of Vaso occlusive crisis received whole blood transfusion therapy. What is the expected complication of this therapy and how can it be prevented?

- A. Continued haemolysis/ Ferritin
- B. Low neutrophil count/ Filgrastim
- C. Hypertension and thrombotic events/ Erythropoietin
- D. Transfusional iron overload/ Deferoxamine

Facts about hypoproliferative anaemia

Deferoxamine removes iron from hemosiderin, ferritin, and transferrin, but not iron from haemoglobin and cytochromes.

Eliminate iron excess without affecting haemoglobin formation.

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Clinical Scenario 5

A multiparous woman with malnutrition was admitted with symptoms of anaemia. Pertinent laboratory values on admission were red blood cell (RBC) count 2.6 × 106/ mm3 (normal, 3.5 − 5.5 × 106/ mm3), mean corpuscular volume 90 fL (normal 80 − 100 fL), haemoglobin 7.2 g/ dL (normal > 12 g/ dL), serum ferritin 7 µg/ dL (normal 30 − 300 µg/ dL), serum vitamin B12 320 pg/ mL (normal > 280 pg/ mL), RBC folate 50 ng/ mL (normal 150 − 800 ng/ mL). The peripheral smear microcytic and macrocytic red blood cells with hypochromia. Which drug treatment would you prescribe this patient?

- A. Vitamin B12 and ferrous sulphate
- B. Erythropoietin and hydroxocobalamin
- C. Folic acid and ferrous sulphate
- D. Folic acid and erythropoietin

Facts about Mixed anaemia

Mixed anaemia comprises micro and macrocytic red cells that average out to give a normal MCV.

The multiparity and poor diet predispose iron and folate deficiency.

- Pregnancy in low social economic settings is another risk factor.

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