HAEMATINICS

HAEMATOPOIETIC SYSTEM: The main components of the haematopoietic system are the blood, bone marrow, lymph nodes and thymus, with the spleen, liver and kidneys as important accessory organs. The most important site of formation of red blood cells in adults is the bone marrow, whereas the spleen acts as their slaughterhouse. The lifetime of a red cell is normally about 120 days. The liver stores vitamin B12 and is involved in the process of breakdown of the haemoglobin liberated when red blood cells are destroyed. The kidney manufactures erythropoietin, a hormone that stimulates red cell production and is used in the anaemia of chronic kidney disease.

Anaemia is characterised by a reduced O_2 carrying capacity *or* reduced haemoglobin content in the blood. The commonest cause is blood loss resulting from menstruation, drug treatment (e.g. with aspirin or other NSAIDs) or pathological processes such as colonic carcinoma or parasitic infestation (especially in developing countries). Pregnancy and child-bearing are important physiological drains on iron reserves.

There are several different following types of major anaemia based on red cell size and haemoglobin content etc. –

• hypochromic, microcytic anaemia (small red cells with low haemoglobin; caused by chronic blood loss giving rise to iron deficiency)

• macrocytic anaemia (large red cells, few in number)

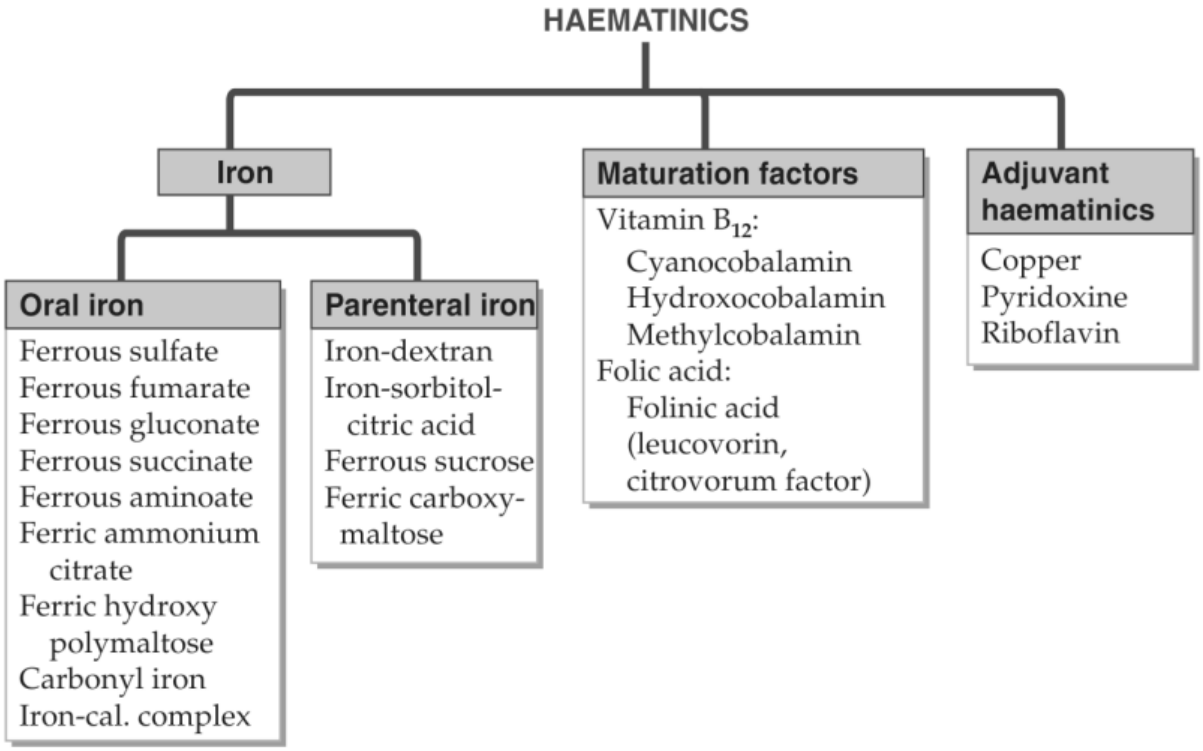
• normochromic normocytic anaemia (fewer normal-sized red cells, each with a normal haemoglobin content)

Further evaluation may include determination of concentrations of ferritin, iron, vitamin B12 and folic acid in serum, which leads to more precise diagnostic groupings of anaemias into –

- Deficiency of nutrients necessary for haematopoiesis, most importantly:
  • iron • folic acid and vitamin B12 • pyridoxine and vitamin C
- Depression of the bone marrow, commonly caused by:
  • drug toxicity (e.g. anticancer drugs, clozapine) • exposure to radiation, including radiotherapy • diseases of the bone marrow (e.g. idiopathic aplastic anaemia, leukaemias)
- Reduced production of, or responsiveness to, erythropoietin (e.g. chronic renal failure, rheumatoid arthritis, AIDS)
- Excessive destruction of red blood cells (i.e. haemolytic anaemia); this has many causes, including haemoglobinopathies (such as sickle cell anaemia)

HAEMATINIC AGENTS

These are the agents required for the formation of blood and treatment of anemia.



Iron is important for the synthesis of haemoglobin, myoglobin, cytochromes and other enzymes.

- Iron is absorbed mostly in the duodenum in the ferrous form (Fe2+). Heme contains the iron in ferrous form and most of the inorganic iron is in ferric form (Fe3+). This must be reduced to ferrous form for absorption. Thus reducing substances like ascorbic acid and also gastric acid (HCl) increases the absorption. On the other hand, substances like alkalies, phosphates, phytates and tetracyclines decrease the absorption.
- After absorption, iron can either be stored as ferritin or it is transported with transferrin to be utilized in the formation of blood. When there is excess of iron in the body, it combines with apoferritin to form ferritin, which remains stored in the mucosal cells
- Parenteral route (i.v., i.m.) is indicated only when oral iron is not tolerated, not absorbed or along with erythropoietin.
- Parenteral iron preparations are iron-dextran and iron-sorbitol-citrate. Former can be given by either i.v. or i.m. routes whereas the latter should not be used intravenously because it will cause rapid saturation of transferrin receptors, which can cause iron toxicity due to more free iron.
- Total iron requirement can be calculated by the formula:

  $$4.3 \times \text{Body weight (kg)} \times \text{Hemoglobin deficit (g/dl)}$$

- The antidote of acute iron poisoning is desferrioxamine. It is given by i.m. injection.

- For chronic iron overload, as occurs in thalassemia patients, oral chelating agent like deferiprone is preferred.

Clinical uses of iron salts

To treat iron deficiency anaemia, which can be caused by:

• chronic blood loss (e.g. with menorrhagia, hookworm, colon cancer);

• increased demand (e.g. in pregnancy and early infancy);

• inadequate dietary intake (uncommon in developed countries);

• inadequate absorption (e.g. following gastrectomy, or in diseases such as coeliac disease, where the intestinal mucosa is damaged by an immunologically based intolerance to the wheat protein gluten)

FOLIC ACID

Liver and green vegetables are rich sources of folate (also known as vitamin B9). In healthy non-pregnant adults, the daily requirement is about 0.2 mg daily, but this is increased during pregnancy. Healthy fetal neural development in particular requires sufficient folate.

Mechanism of action: Reduction of folic acid, catalysed by dihydrofolate reductase in two stages yields dihydrofolate (FH2) and tetrahydrofolate (FH4), co-factors which transfer methyl groups (1-carbon transfers) in several important metabolic pathways. FH4 is essential for DNA synthesis because of its role as co-factor in the synthesis of purines and pyrimidines. It is also necessary for reactions involved in amino acid metabolism. FH4 is important for the conversion of deoxyuridylate monophosphate (DUMP) to deoxythymidylate monophosphate (DTMP). This reaction is rate limiting in mammalian DNA synthesis and is catalysed by thymidylate synthetase, with FH4 acting as methyl donor.

Pharmacokinetic aspects: Therapeutically, folic acid is given orally and is absorbed in the ileum. Methyl-FH4 is the form which is usually carried in blood and which enters cells. It is functionally inactive until it is demethylated in a vitamin B12-dependent reaction. Folate is taken up into hepatocytes and bone marrow cells by active transport. Within the cells, folic acid is reduced and formylated before being converted to the active polyglutamate form. Folinic acid, a synthetic FH4, is converted much more rapidly to the polyglutamate form.

Adverse effects: Unwanted effects do not occur even with large doses of folic acid – except possibly in the presence of vitamin B12 deficiency, when it is possible that administration of folic acid may improve the anaemia while exacerbating the neurological lesion. It is therefore important to determine whether a megaloblastic anaemia is caused by folate or vitamin B12 deficiency and treat accordingly.

• Deficiency of folic acid results in megaloblastic anemia that is indistinguishable from that due to vitamin B12 deficiency.

• Main uses of folic acid are in the treatment of megaloblastic anemia due to folic acid deficiency (dietary, due to malabsorption, phenytoin therapy, chronic alcoholism etc.). It is also indicated in pregnancy to prevent neural tube defects in the fetus. It should be started as soon as the pregnancy is diagnosed.

• Leucovorin (folinic acid, formyl THFA or citrovorum factor) can be used to prevent the toxicity of methotrexate

Clinical uses of folic acid and vitamin B12 (hydroxocobalamin)

Folic acid (vitamin B9)

• Treatment of megaloblastic anaemia resulting from folate deficiency, which can be caused by:

– poor diet (common in alcoholic individuals)

– malabsorption syndromes

– drugs (e.g. phenytoin).

• Treatment or prevention of toxicity from methotrexate, a folate antagonist.

• Prophylactically in individuals at hazard from developing folate deficiency, for example: – pregnant women and before conception (especially if there is a risk of birth defects) – premature infants – patients with severe chronic haemolytic anaemias, including haemoglobinopathies (e.g. sickle cell anaemia).

Vitamin B12 (hydroxocobalamin)

• Treatment of pernicious anaemia and other causes of vitamin B12 deficiency.

• Prophylactically after surgical operations that remove the site of production of intrinsic factor (the stomach) or of vitamin B12 absorption (the terminal ileum)

Vitamin B12, also called cobalamin, corrects pernicious anaemia.

- The vitamin B12 preparation used therapeutically is hydroxocobalamin, derived from cultured microorganisms.
- Vitamin B12, complexed with intrinsic factor, is absorbed by active transport in the terminal ileum. Healthy stomach secretes a large excess of intrinsic factor, but in patients with pernicious anaemia (an autoimmune disorder), or following total gastrectomy, the supply of intrinsic factor is inadequate to maintain vitamin B12 absorption in the long term. Surgical removal of the terminal ileum, for example, to treat Crohn's disease, can also impair B12 absorption.
- Vitamin B12 is carried in the plasma by binding proteins called transcobalamins. It is stored in the liver, the total amount in the body being about 4 mg.

Mechanism of action: Vitamin B12 is required for two main biochemical reactions in humans:

1. **The conversion of methyl-FH4 to FH4**. The enzyme that accomplishes this (homocysteine–methionine methyltransferase) requires vitamin B12 as co-factor and methyl-FH4 as methyl donor (needed for DNA synthesis).
2. **Isomerisation of methylmalonyl-CoA to succinyl-CoA**. This isomerisation reaction is part of a route by which propionate is converted to succinate

Vitamin B12 is used for treatment of megaloblastic anemia (i.m. or s.c. for pernicious anemia due to deficiency of intrinsic factor and orally for other causes), for correcting neurological abnormalities in diabetics etc. (methylcobalamin is used) and also for treatment of tobacco amblyopia (hydroxocobalamin is used, it combines with cyanide to form cyanocobalamin).

Haematopoietic growth factors in blood cell differentiation. Various preparations of the factors shown in bold are in clinical use. Most T cells generated in the thymus die by apoptosis; those that emerge are either CD4 or CD8 T cells. The colours used for the mature blood cells reflect how they appear in common staining preparations (and after which some are named). CSF, colony stimulating factor; G-CSF, granulocyte CSF; GM-CSF, granulocyte–macrophage CSF; IL-1, interleukin-1; IL-3, interleukin-3 or multi-CSF; M-CSF, macrophage CSF; SCF, stem cell factor.