Drug treatment of anemia

1-Iron.  2-Vitamin B12.  3-Folic acid.  4-Erythropoietin

1-Iron

Causes of iron deficiency anemia (IDA)

1-Increased requirement (infants, children, pregnant, lactating)
2-Reduced intake (malnourished, vegetarians)
3-Increased loss (menstruation, 30mg per month, GIT bleeding)

Iron distribution in normal adults - Total about 4444 mg in men, 2222 mg in women

1-Hb
2-Myoglobin
3-Enzymes
4-Transport-transferrin
5-Storage - ferritin & other forms

Kinetics

Absorption
-Duodenum and jejunum (terminal ileum can absorb iron).
10% of the administered iron is absorbed in normal conditions - Maximal 25% in treatment of deficiency states, 100 mg per day can be absorbed in these cases

Transport
-Transferrin

Storage
-Ferritin
-Intestinal cells
-RES (macrophages)

Elimination
No mechanism (1 mg per day is lost during intestinal cells and skin exfoliation)
Diagnosis of IDA

-Hb
-Blood film -hypochromic microcytic-
-Serum Iron
-TIBC (total iron binding capacity).
-S.Ferritin

Treatment of IDA

Oral
- Ferrous sulphate
- Ferrous gluconate
- Ferrous fumarate
- Others

Parenteral
- Iron dextran
- Iron sucrose
- Iron carboxy maltose
- Others

Toxicity of iron - Adverse effects or side effects -

-Acute toxicity
  - Necrotizing gastroenteritis ending with Shock ... Metabolic acidosis ... Coma ...
  - Death.

-Chronic toxicity

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2- Vitamin B12

Structure, source and RDA

-Cyano cobalamine
-Hydroxo cobalamine

B12 is synthesized only by bacteria (cannot be synthesized by multicellular organisms!)

Recommended daily allowance (RDA) = 1 ug

Kinetics

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Absorption
Intrinsic factor - a protein synthesized by parietal cells of the stomach is needed for B12 absorption in the intestine.

Transport
Transcobalamin

Storage
Liver in a normal individual has a large store which is enough for about five years before the manifestations of B12 deficiency appear as subacute combined degeneration of the spinal cord and as pernicious anemia.

Dynamics
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1- Methylmalonyl coA conversion to succinyl coA
2- Homocysteine conversion to methionine (this reaction is linked to folic acid metabolism and synthesis of deoxythymidylate (dTMP), a precursor required for DNA synthesis).

Clinical uses
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1- Megaloblastic anemia after gastrectomy. -- No IF -- No B12 absorption.
2- Megaloblastic anemia after auto immune destruction of the parietal cells of the stomach-called pernicious anemia.
3- Subacute combined degeneration of the spinal cord (scdc) (No B12 -- no homocysteine conversion to methionine -- no myelin sheath on the neurones - scdc).

Toxicity
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No significant toxicity.

3- Folic acid (FA)

Structure
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Folic acid = pteroyl glutamic acid = (pteridine + paba + glutamic acid)
FA is reduced to dihydro FA by dihydro folate reductase (folate reductase).
DHF is reduced further by DHF reductase to tetrahydrofolic acid (THF).
THF can subsequently be transformed to folate cofactors possessing one carbon unit donated to a suitable acceptor by various enzymatic reactions

FA provide precursors for the synthesis of 1-purines
2-Amino acids
3-DNA

Kinetics
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RDA = 0.2 mg
the richest sources are
1-Yeast
2-Liver
3-kidney
4-Green vegetables

Storage is mainly in the liver (about 10 mg) so megaloblastic anemia develops rapidly after FA deficiency because of the paucity of body store and the high daily requirement.

Absorption
Jejunum
1-FA
2-Methyltetahydrofolate (After absorption, distribution and entering the cell this form must be converted to THF by the demethylation reaction that requires vitamin B12.

Dynamics
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1 - dUMP conversion to dTMP. In this reaction the enzyme thymidylate synthase catalyzes the transfer of the one-carbon unit of methyleneTHF to deoxyuridine monophosphate (dUMP) to form deoxothymidinephosphate(dTMP). dTMP is needed for DNA synthesis -not dUMP-
2 - Purine synthesis
3 - Amino acids synthesis

Clinical uses
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1-Megaloblastic anemia resulting from FA deficiency which is microscopically indistinguishable from megaloblastic anemia of B12 deficiency (but can be distinguished by finding low RBC folate levels). scdc is seen only with B12 def. not FA def. Vitamin B12 deficiecy must be ruled out before using FA as the sole agent in the the treatment of megaloblastic anemia.

2-FA supplementation for prevention of its deficiency should be considered in high risk patient including
   -Pregnant women (neural tube defect as spina bifida may result from maternal FA deficiency).
   -Alcoholics (There is evidence that alcohol interferes with absorption and metabolism of FA)
   -Hemolytic anemia
- Liver disease
- Certain skin diseases
- Patients on renal dialysis

**Toxicity**

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FA has no recognized toxicity.

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Figure 33-2. Enzymatic reactions that use folates. Section 1 shows the vitamin B₁₂-dependent reaction that allows most dietary folates to enter the tetrahydrofolate cofactor pool and becomes the "folate trap" in vitamin B₁₂ deficiency. Section 2 shows the dTMP cycle. Section 3 shows the pathway by which folate enters the tetrahydrofolate cofactor pool. Double arrows indicate pathways with more than one intermediate step.
4- Erythropoietin

Chemistry
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Erythropoietin is produced by the kidney. The reduction in its synthesis is responsible for the anemia of renal failure.
Epopoietin alfa is a recombinant human erythropoietin.
Darbopoietin alfa is a glycosylated form of erythropoieten with a longer duration of action.

Dynamics
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Endogenous erythropoietin is produced by the kidney in response to tissue hypoxia.
Erythropoietin stimulates erythroid proliferation by interacting with specific erythroietin receptors on red cell progenitors.

Clinical uses
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Erythropoietin is used for the anemia associated with renal failure.
Erythropoietin is used in selected patients for the treatment of anemia due to primary bone marrow disease as aplastic anemia, leukemia and anemias secondary to cancer chemotherapy, HIV treatment and cancer.

Toxicity
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Minimal and usually results from excessive increase in Hb and hematocrit manifested as hypertension and thrombosis, minimized by slowly raising the Hb and hematocrit and by monitoring the blood pressure.