بسم الله الرحمن الرحيم

Drug treatment of anemia (Part 1)

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2026

INTRODUCTION

Red blood corpuscles (RBCs) carry oxygen to tissues via hemoglobin.
The most important site of formation of red blood cells in adults is the **bone marrow**.
RBCs count in healthy adults is balanced by production of new cells.

Anemia is a condition in which the body does not have enough healthy red blood cells.

Clinical Presentation of Anemia
Pallor – Fatigue – Dizziness – Dyspnea.
These symptoms will lead to cardiovascular adaptation in the form of tachycardia , increased cardiac output and vasodilatation which may worsen the situation in patients with cardiovascular disease.

Types of Anemia

Classification depends on RBC size, hemoglobin content and microscopic examination of blood smear.

Two famous types of anemia:

1- Hypochromic, microcytic anemia (small red cells with low hemoglobin; caused by iron deficiency).

2- Macrocytic anemia (large red cells, few in number; caused by vitamin B12 or folic acid deficiency).

Other types: Aplastic anemia, anemia of chronic diseases, Congenital forms of anemia, hemolytic anemia and autoimmune causes.

Megaloblastic anemia

1-Vitamin B_{12} and anemia

Vitamin B_{12} (cobalamin)

Vitamin B12 is needed for many biochemical reactions in humans.

Vitamin B12 is sometimes called extrinsic factor

- vitamin B12 is not synthesized by animals or plants. The chief dietary source of vitamin B12 is microbially derived vitamin B12 in meat (especially liver), eggs, and dairy products.
- Vitamin B_{12} binds with the intrinsic factor (secreted from gastric parietal cells) and the complex is absorbed in the terminal ileum.
- In the circulation, it binds to transcobolamin II to be stored in the liver.
- Stored forms of Vit B 12 in the liver can supply the body for more than 3 years after absorption is stopped
- The active forms of vit B 12 are ***methylcobalamin*** & ***deoxy-adenosylcobalamin***.

Biochemical consequences of vitamin B12, deficiency

1- Decrease conversion of N5-methyltetrahydrofolate to tetrahydrofolate.

➢ The accumulation of N5-methyltetrahydrofolate and depletion of tetrahydrofolate in vitamin B12 deficiency is called "methylfolate trap."

❑ The megaloblastic anemia of **vitamin B12 deficiency** can be **partially corrected** by ingestion of **large amounts of folic acid (which is** educed by dihydrofolate reductase to tetrahydrofolate used for purine & DNA synthesis).

2- Accumulation of homocysteine due to ↓ its conversion to methionine.

❑ Elevated serum homocysteine establish diagnosis of vit B12 deficiency.

❑ The disruption of the methionine synthesis pathway is the cause of neurological manifestations.

3- Decrease conversion of methylmalonyl-CoA to succinyl-CoA.

❑ The increase in serum and urine concentrations of methylmalonic acid can be used to support a diagnosis of vitamin B12 deficiency .

N.B. Whatever the biochemical explanation for neurologic damage, the important point is that administration of folic acid in cases suffering from vitamin B12 deficiency will not prevent neurologic manifestations even though it will largely correct the anemia caused by the vitamin B12 deficiency.

Causes of vitamin B12 deficiency anemia:

1-The main cause of deficiency is failure of secretion of the intrinsic factor by the gastric mucosa as in cases of pernicious anemia where there is atrophic gastritis with achlorhydria and failure of secretion of intrinsic factor.

➢ These patients frequently have auto-antibodies to intrinsic factor.

2- After intestinal resection.

3- Insufficient intake of Vit B 12 in Diet (e.g. strict vegetarian diet).

❑ Pathology: hypercellular bone marrow with an accumulation of megaloblastic erythroid and other precursor cells

Manifestations of vitamin B12 deficiency :

1-Megaloblastic anemia with mild leukopenia or thrombocytopenia.

2- Neuronal demyelmation: paresthesias and muscle weakness that progresses to spasticity, ataxia, and other CNS dysfunctions (if not treated).

➢ Immediate treatment with Vit B12 should start to avoid irreversible neurological defects (cell death in spinal column and cerebral cortex).

❑ Correction of vitamin B12 deficiency arrests the progression of neurologic disease, but it may not fully reverse neurologic damage.

N.B. Although most patients with neurologic abnormalities caused by vitamin B12 deficiency have **megaloblastic anemia** when first evaluated, occasional patients have few or even no hematologic abnormalities.

❑ The Schilling test, which measures absorption and urinary excretion of radioactively labeled vitamin B12, can be used to further define the mechanism of vitamin B12 malabsorption when this is found to be the cause of the megaloblastic anemia.

Treatment of vitamin B_{12} deficiency anemia:

1-Cyanocobalamin or ***hydroxocobalamin***

- These are stable formulations and changed to the active forms (methylcobalamin & deoxyadenosylcobalamin).
- In patients with pernicious anemia, parenteral therapy is used because oral therapy is ineffective as the cause is usually defect in site of absorption.
- Cyanocobalamin and hydroxocobalamin are used I.M. or deep S.C. but not I.V.

2- Combination of **oral vitamin B_{12}** and **intrinsic factor** can be used in patients with pernicious anemia who refuse the injection but the formation of intraluminal **antibodies to human intrinsic factor** may interfere with the absorption of vitamin B_{12}.

Oral and sublingual preparations containing Vitamin B12 are available.

Hydroxocobalamin is preferred as it is highly bound to proteins and so it remains longer in the circulation with sustained effect.

Dose and duration of treatment:

- 100-1000 µg / day for 1-2 weeks I.M.
- then 100 -1000 µg / week for 1 month (but for 6 months if there is neurological defects)
- then 100 µg /month for life.

➢ Now vitamin B_{12} is available as spray and gel for intranasal use as a maintenance therapy in cases of pernicious anemia.

- Both diabetes & vitamin B12 deficiency can independently lead to neuropathy.
- it may be advisable for a person with diabetes to take vitamin B12 supplements
- Metformine may decrease Vit B12 absorption

2- Folic acid deficiency anemia

Metabolism of folic acid:

- Folic acid is found in most fruits, vegetables, liver and yeast.

- It is inactive and reduced by dihydrofolate reductase to dihydrofolic acid then to tetrahydrofolate which is a cofactor that enters in synthesis of **DNA and RNA**.

- Folinic acid (leucovorin) is converted directly to tetrahydrofolate.

- Folic acid is absorbed in upper small intestine then it is reduced and methylated to methyl tetrahydrofolate.

Causes of folic acid deficiency anemia:

1. Inadequate intake.
2. Increase in requirements as in pregnancy, hyperthyroidism and chronic dialysis.
3. Inhibition of absorption as in malabsorption syndrome, the use of some drugs as phenytoin, phenobarbital and oral contraceptive.
4. Inhibition of dihydrofolate reductase enzyme by methotrexate, trimethoprim and pyrimethamine.

Manifestations of folic acid deficiency anemia:

Deficiency of folic acid leads to megaloblastic anemia without neurological manifestations.

Treatment of folic acid deficiency anemia:

It is treated by oral folic acid as oral therapy is well absorbed even in presence of malabsorption.

It is used for 4-6 weeks which is a sufficient time for correction of anemia and replenish body stores.

I.M. injection is used in severe ill patients followed by oral maintenance therapy.

Treatment should be continued until correction of the cause of deficiency, otherwise treatment should be continued for life.

In case of severe deficiency of vitamin C, oral folic acid is ineffective.

Folinic acid is used only in cases of obstruction of folate activation as by the use of methotrexate or trimethoprim.

Hematopoietic growth factors

These are hormone-like glycoprotein that regulate the division and maturation of the progeny blood cells in bone marrow.

1- Erythropoietin:

It is produced by the kidney in response to hypoxemia and regulates the formation of RBCs.

Pharmaceutical **Erythropoietin** is prepared by recombinant DNA technology and used **S.C. or I.V.** for:

1- Anemia of chronic renal failure (due to decrease in erythropoietin release and excess loss of RBCs during dialysis).

2- Anemia of AIDS, cancer, rheumatoid arthritis and anemia occurs in premature infants.

2- Epoetin alfa (agonist of erythropoietin receptors) and **Darbepoetin alfa** (long acting form) can be used as erythropoietin.

2- Myeloid growth factors:

It is produced by fibroblasts, endothelial cells, macrophages and T lymphocytes in response to systemic infection, it regulates the formation of WBCs and include:

A. Filgrastim is a synthetic Granulocyte-colony stimulating factor (G-CSF), it affects neutrophils.
   - ❑ Pegfilgrastim: Long-acting form of filgrastim

B. Sargramostim is a synthetic Granulocyte /macrophage-colony stimulating factor (GM-CSF), it affects neutrophils, monocytes and eosinophils.

Myeloid growth factors are given S.C. or I.V. for:

1- Patient suffering from **aplastic anemia.**

2- After **bone marrow transplantation**.

3- To prevent and treat bone marrow depression of **cancer chemotherapy** .

3- Megakaryocyte growth factors and related drugs:

They regulate the formation of platelets and include:

1-Interleukin 11 (oprelvekin)

Given parenterally in treatment of thrombocytopenia.

2-Thrombopoietin

Given parenterally in treatment of thrombocytopenia.

3- Thrombopoietin receptor agonists (romiplostim and eltrombopag) for patients with idiopathic thrombocytopenic purpura.

4- Fostamatinib is an **orally active prodrug** approved for use in patients with **chronic immune thrombocytopenia** who have had an inadequate response to other therapies.

It decreases antibody-mediated platelet destruction.


THANK YOU!