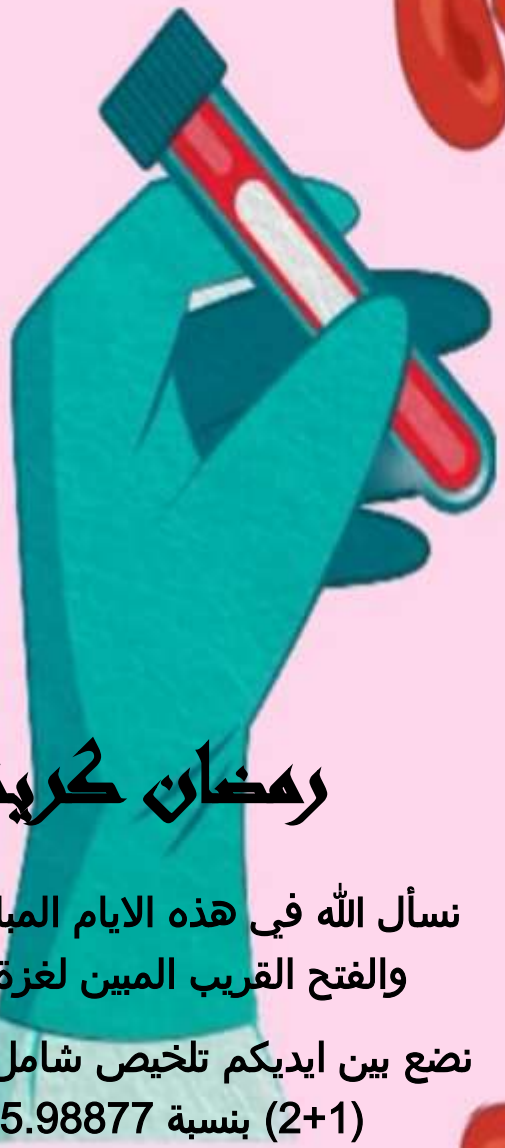
HEMATOPOIETIC & LYMPHATIC SYSTEM



SUBJECT : Pharma. Summary

LEC NO. : Lecture(1+2)

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نسأل الله في هذه الايام المباركة الفرج
والفتح القريب المبين لغزة العزة

نضع بين ايديكم تلخيص شامل لمحاضرة
(2+1) بنسبة 95.98877%

DRUG THERAPY OF IRON-DEFICIENCY ANEMIA
(Microcytic Hypochromic Anemia)

Anemia: is defined as a **low hemoglobin (Hb) concentration** due to reduced production or increased loss of RBC. The WHO defines anemia as **in male(Hb<13) , female(Hb<12)**

Types of anemia:

1. **Deficiency Anemia**
   A-Iron deficiency anemia: due to iron deficiency
   B-Megaloblastic anemia: due to vitamin B12, intrinsic factor, or folic acid deficiency.
2. **Aplastic anemia**: due to damage of bone marrow
3. **Hemolytic anemia**: due to destruction of red cells

Information

Iron Absorption

- **Iron intake**:from plant-derived foods, in the form of non-heme iron (Fe^{3+} ferric), and from animal-derived foods, in the form of heme iron (Fe^{2+}ferrous)
- **Absorption site**:in the duodenum and in the first portion of the jejunum (acid medium ↑solubility)

Factors Enhancing Iron Absorption:1-Infancy, adolescence and in iron-deficiency anemia (↑demand)
2- Ascrobic acid, HCl & succinic acid (↑absorption ferric → ferrous).

Factors Reducing Iron Absorption:1-Patholigical:Gastric resection and malabsorption syndrome
2-Medications:Desferrioxamine (chelates iron)/ Tetracyclines & iron bind together(↓absorption of both).
3-Nutritions:Antacids/ Tannic acid (precipitates iron) /Ca in dairy food(↓iron absorption)/ Phosphates & oxalates (form insoluble iron complexes).

Iron Transport:The Function of Hepcidin?(a protein synthesized by the liver)1-regulates iron release from enterocytes and 2-iron recycling by macrophages, and it may contribute to the anemia of chronic diseases

Iron-Deficiency Anemia due to

↑ **Demand**: premature infants/children/ adolescence/ pregnant and lactating women.
↓**Decrease Absorption**: after gastrectomy & in malabsorption syndrome.
Drain(Chronic) blood loss: occult GIT bleeding/heavy menstrual bleeding/ during hemodialysis/ancylostomiasis.
↑ **in blood formation**: during treatment of severe pernicious anemia with vitamin B12 (depletion of iron stores), during treatment with erythropoietin{renal failure} (formation of RBCs at a high rate).

((Treatment of the cause is essential))

Indications of Iron Therapy

Prophylactic of the occurrence of iron-deficiency anemia (IDA):
30-60 mg/day elemental iron (↑ **Demand**: premature infants/children/ adolescence/ pregnant and lactating women)
Treatment of IDA: 200-400 mg/d elemental iron in 2-3 divided doses/d
{In Healthy individuals **10%** of Iron intake is absorbed ,While in Iron Daficiency patiets (IDA) **25%** of Iron intake is absorbed}

Iron Toxicity

	Acute Iron Toxicity	Chronic Iron Toxicity
Mostly Occures in	**(CHILDREN)** 1.**GIT (up to 1h)**: Abdominal pain- nausea- vomiting- bloody diarrhea. 2 .**Shock & lethargy (up to 6h)**: dyspnea- cardiovascular collapse 3. **Improvement (up to 6-12h)**: as iron is absorbed into blood. 4. **Systemic (up to 12-60h)**: metabolic acidosis- convulsions- coma &death	1. Patients **receiving many red cell** transfusions. (haemolyticanemia 2. Patients with **hemochromatosis**; an inherited disorder characterized by increase Fe absorption hemosiderosis (Fe3+ precipitation in vital organs)
Treatment	**Raw egg or milk** : bind & precipitate iron as albuminate or caseinate until a chelating agent is available (Urgent temporarily procedure) **Deferoxamine (1-2 g IM or IV)**: chelates iron promoting its excretion in urine **Gastric lavage with bicarbonate solution** form insoluble iron salts. Then, **deferoxamine (5 g in 100 ml water)** swallowed or through stomach tube **IV infusion of saline, dextrose or bicarbonate**:correct water & electrolyte disturbance	1. **Venesection** (if **NO** anemia) :repeated weekly (a single **venesection of 500 ml blood removes 200 mg iron**) 2. **Deferoxamine** IM or **SC**. 3. Large intake of **tea** : **tannins bind** iron.

DRUG THERAPY OF IRON-DEFICIENCY ANEMIA

Iron Therapy (Oral Parenteral (IV, IM))

	Oral Iron Therapy	Parenteral Iron Therapy
Indications	**First** Treatment of choice	(Causes **of failure of oral** iron therapy) 1.**Noncompliance** to oral therapy (severe GIT disturbance or ulceration) 2.**Malabsorption syndrome** causes failure of iron absorption 3.**Severe anemia** in malignancy 4.**Renal failure**
Preparations	Ferrous sulfate(20%),Ferrous gluconate(12%) and Ferrous fumarate(33%)• New agents: polysaccharide-iron complex, carbonyl iron(100%),Heme iron polypeptide(Sustainable Release effect, low Adverse effect, High doseage, more expensive) • **Different Fe salts provide different amounts of elemental** (**Iron salts are usually used as ferrous iron is efficiently absorbed**.)	1-Iron dextran 2-Iron sucrose complex & Iron sodium gluconate complex. 3-Newer preparations: Ferric carboxymaltose & Ferumoxytol(Low allergistic effect, Low adverse effect) • **Given by deep IMI or by IV infusion** (as a total dose infusion, TDI).
Therapeutic (Period DOSE)	Continue iron till **Hb is normal** (1-2 months) & for an extra(2-4 months) to **replenish stores**	**Calculation of Parentral Iron** (to correct anemia & replenish stores) **Total iron deficit (mg)**=[Body weight (kg) x [Target Hb - Actual Hb] (g/l)x2.4+ 500 (mg)]{Parenteral therapy involves adiminstering the **total dose to replenish iron stores initially**,Then gradually the body starts to **restore Fe from the stores** to correct anemia}
Advantages	Effective & cheap	**Advantages of TDI** :1-Avoids **non-compliance** of the patient. 2- Avoids **unpleasant effects of IMI.** 3) Allows delivery of the entire dose of iron necessary to correct iron deficiency at one time. ❖ **The initial 25 ml should be infused slowly** (as a test dose) and the patient should be **observed for allergic reaction { Allergic Test}**
Adverse Effects	**GIT disturbances**: nausea, epigastric pain, constipation (given after meals - start with small dose then gradually increase). **Black stools** (mask diagnosis of GI bleeding). **Black staining of teeth** (iron sulfide in mouth)	IM: **local pain** - tissue staining. • IV: headache, fever, urticaria, lymphadenopathy **& anaphylactic shock**
Monitoring iron therapy	A**. Clinically: improve** the patient's symptoms and signs. B. **Lab**. Investigations:1. Reticulocyte counts:↑ **(1 week**) 2. Hb:↑ (**1 gm/10-15 days**) 3. Serum ferritin: > 50 ug/dl (stores) **(after 4-6 months**){ The Therapeutic Period is **SAME** to Both routes of administration, However in **ORAL** adminstration **initial clinical improvement** takes place, while **PARENTERAL** adminstatration initates an **increase in Serum ferritin levels**}	

Aplastic Anemia

Treatment of Anemia

1-**Blood transfusion** to replace lacking components
2-**Treatment** according to **cause** (if known).
3- **Corticosteroids**: **reduce** bleeding caused by **thrombocytopenia**.
4- **Broad-spectrum antibiotics**, e.g. penicillins to treat infections.
5- **Bone marrow transplantation (Treatment of Choice)** followed by immunosuppression to **prevent graft** rejection.
6- **Erythropoietin**. (IV or SC)
• **Regulator** of erythropoiesis (acts on stem cells).
• **Used** in anemia of (chronic renal failure & severe anemia of cancer & AIDS).
• It **decreases** the need for **transfusion** as it **elevates red blood cell** level.

Anemia of Chronic Disease

The Cause of Anemia

• **Chronic infection and inflammation** with : ↑release of **cytokines**➪ **stimulate** the release of **hepcidin** from the liver➪ **prevent absorption & release** of iron from its storage sites (**sequestrated anemia**).

Differences from IDA

• It is **a functional iron deficiency anemia**
• **Differs** from iron deficiency anemia :there is **normal or high serum ferritin**.
• **Not treated with iron** but its treatment is to **treat infection & inflammation**

MEGALOBLASTIC ANEMIA
(Vitamin B12+Pernicious Anemia)

Informations

- **Cobalt-containing** compound **synthesized** by **bacterial flora** in colon.
- **Called extrinsic** factor to differentiate it from an **intrinsic factor** (**a glycoprotein formed** by parietal cells, necessary for vitamin **B12 absorption**).

Functions of Vitamin B12(It is essential for):

1-Cell growth and replication (**DNA synthesis**),**Erythropoiesis** and cell maturation

2- **Neurological** Function **Maintenance** of normal **myelin sheath**

3- **Normal metabolic functions of folate**

Causes of B12 deficiency

1.Decreased intake (**RARE** Why?)

[If vitamin B12 absorption is stopped, it takes **5 years for megaloblastic** anemia to **develop** since it **daily requirement is 2 μg & body store is relatively high**]

2. Decreased absorption:

A-**D**ecreased **intrinsic** factor (pernicious anemia)[congenital, autoimmune, after gastrectomy]

B-**D**rugs(Prevent the absorption of B12): Neomycin, colchicine and antiepileptics

C-**T**erminal ileum disease e.g. Crohn's disease.

3. **I**ncreased demands: pregnancy, chronic hemolysis

4.**I**ncreased consumption: Diphyllobothrium latum

Pernicious Anemia

It is a **SEVERE form of Megaloblastic Anemia** due to **deficiency of intrinsic factor**

Characterisstics:

1. **Megaloblastic anemia** (large red cells highly susceptible to destruction).[**Blood**]
2. **Subacute** combined degeneration of brain, spinal cord & peripheral nerves.[**Nervous System**]
3. **Atrophic** gastritis [achlorhydria patients"Low levels of HCL"]

Therapeutic uses of B12

A. MEGALOBASTIC Anemia (plus **Folic acid 5 mg**/d) [**Treatment of the cause**]

1. **Pernicious anemia**: vitamin B12 is **given for life by IMI**.
- **Initial** therapy: **1000 μg/day for 1-2 week to replenish stores**.
- Then **1000 μg/week till normal blood count**.
- Then **Maintenance** therapy: **1000 μg/month for life**.

2. Megaloblastic anemia due to **diphylobothriasis (vitamin B12 + praziquantel).**

3. **Drug-induced** megaloblastic anemia

B. NEUROLIOGICAL Conditions

- Peripheral neuritis in **diabetes**(B12 is Water-Soluble) & retrobulbar neuritis in **heavy smokers**.

{NEVER give Folic acid ALONE in B12 deficiency as it↑↑ the Neurological Complications}

Informations

- **Source**: liver, yeast and green vegetables.
- **Essential for DNA synthesis**.
- **{B12 is essential for activation of folic acid**. So **B12 deficiency is often associated with folic-acid-deficiency anemia}**.
- **No neurological abnormalities** are associated with folate deficiency

Causes of Folic Acid Deficiency

1.**I**nadequate dietary supply (**common**)

[**Folate deficiency** develops **more rapidly** than vitamin B12 deficiency since **daily requirement is high and body store of folate is low**.]

2. **I**ncreased demand: e.g. pregnancy, lactation.
3. **D**ecreased absorption: **malabsorption** syndrome

Drug-induced folic acid deficiency VIP

A. Antiepileptics & oral contraceptives (**interfere** with folate **absorption**).

b. Methotrexate, sulphonamides (**inhibit** dihydrofolate **reductase enzyme** leads to the **inhibition of folic acid activation**) [**Treated by folinic acid**].

Therapeutic uses of folic Acid

1.Decreased intake(Nutritional megaloblastic anemia,Malabsorption syndrome). 2.increased demands(In alcoholics and pregnant women). 3. Patients with liver disease & with hemolytic anemia. 4.Patients on dialysis (as folic acid is removed each time). 5. With anticonvulsant drugs

MEGALOBLASTIC ANEMIA
Folic Acid (Pteroylglutamic Acid)

Preparations of B12

A. Cyano**cobalamin**

B. Hydroxo**cobalamin** (preparation of **choice**):

1. More **S**lowly **absorbed**.
2. **S**lowly **excreted.**
3. **M**ore bound to **plasma proteins**.
4. **M**ore sustained **rise in serum cobalamin**