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4 43
haematology Team

MED 443
King Saud University

Anemia

GNT Block

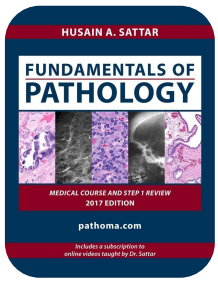
COLOR INDEX:

- Main text
- Dr. Notes
- Male's text
- Femal's text
- Important
- Extra

Editing file:

Objectives

- To understand the normal control of erythropoiesis
- To understand the pathophysiology of anemia
- To recognize the general features of anemia
- To understand the basis of anemia classification
- To understand iron metabolism, how iron deficiency and anemia of chronic disease may arise and how to manage it



Click on PATHOMA for a revision and more info!

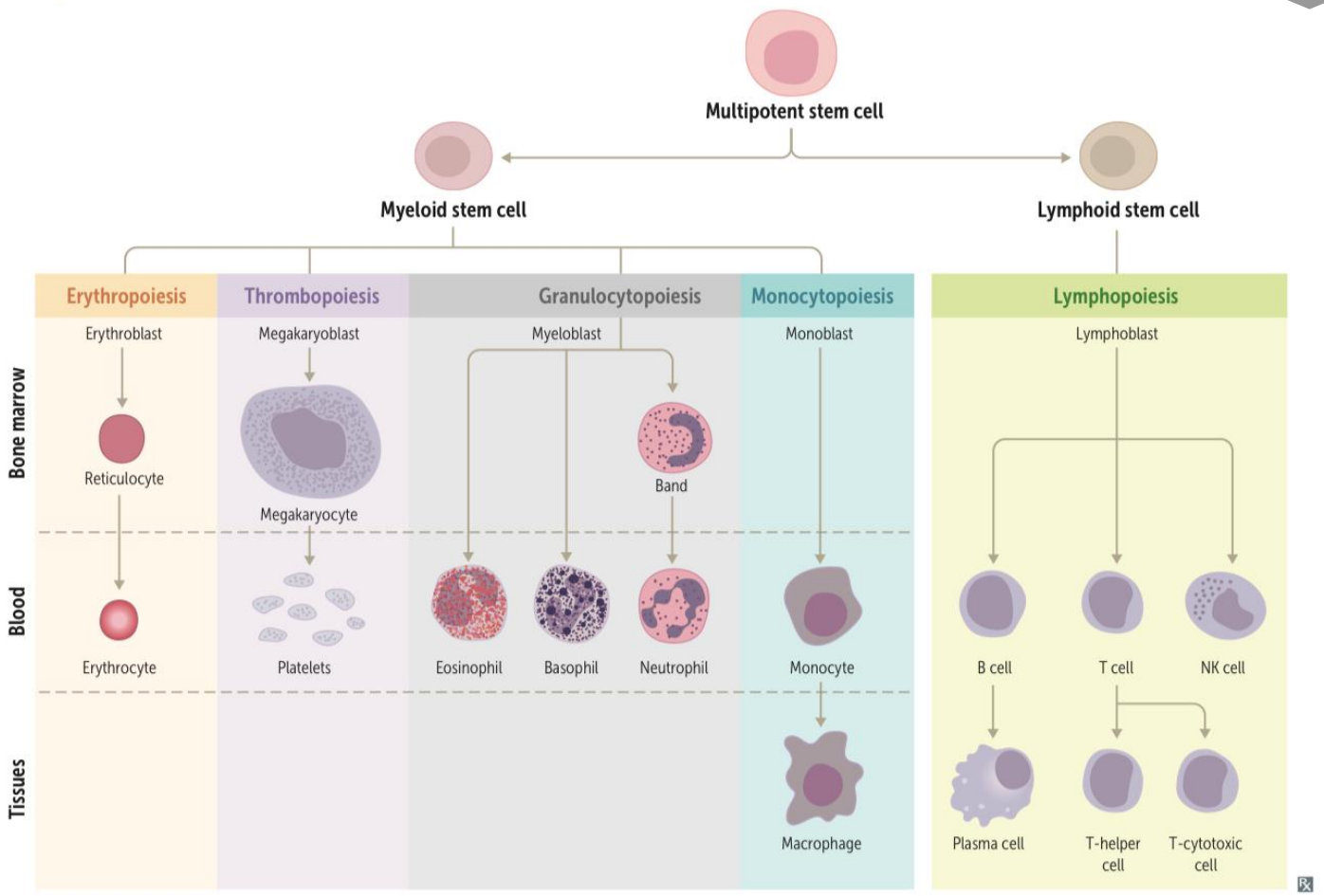
Our YouTube's playlist for this lecture!

This lecture was given by: Dr. Mansour Al jabry and prof. Fatma Al Qahtani

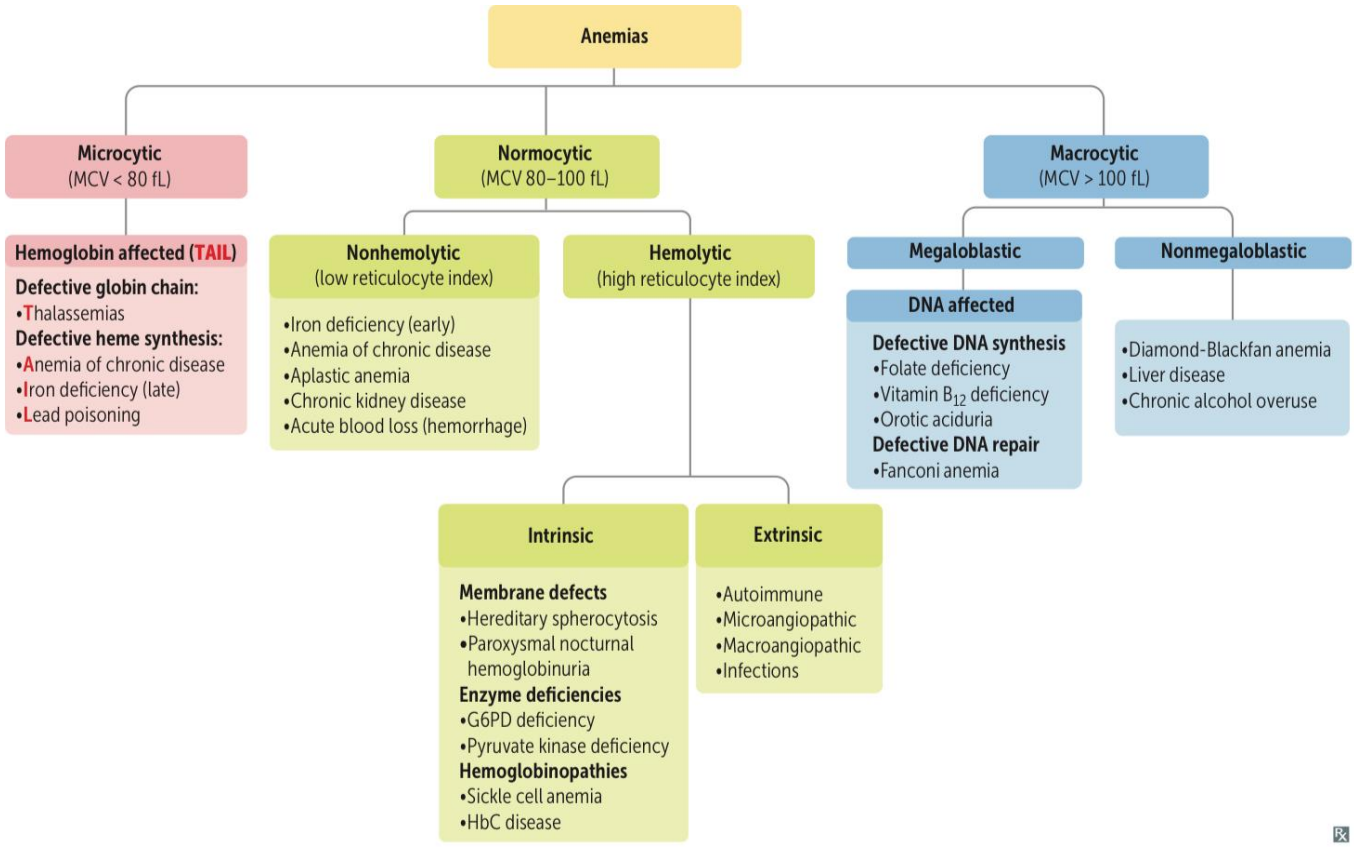
*No objectives was found in new male slides

EXTRA

Quick reminder of Hematopoiesis



Introduction to anemia



Introduction

Hemoglobin

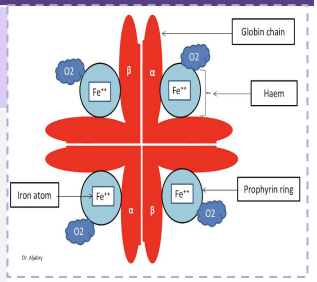
Function

Hemoglobin main important molecule in anemia is the protein molecule in RBC. that carries O2 from the lungs to the body's tissues and returns carbon CO2 from the tissues back to the lungs.

- Other function,Hemoglobin **maintains the shape of RBCs**
  It also maintains the blood pH. (Buffering effect)

Structure

- There are many types of hemoglobin. HbA is the major hemoglobin found in Adults.
- HbA is made up of two alpha (α) and two beta (β) subunits. Will be discussed in biochemistry lecture:)

Hemoglobin structure Important for RBCs				
Heme (Non protein)		Globin chain (protein)		
Iron binding O2 (Ferrous state, Fe2+)	porphyrin ring	2 α chains	2 β chains	

Quick recap - discussed in next slides…

What is the difference between hematopoiesis and erythropoiesis?

Hematopoiesis is the formation of mature blood cells whereas erythropoiesis is the formation of mature erythrocytes (red blood cells)

Introduction
Hematopoiesis

Hematopoietic Stem Cells (HSCs):

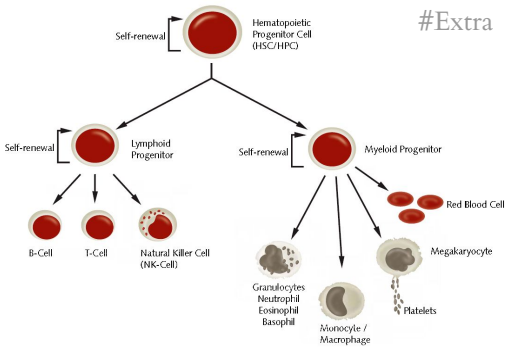
HSCs: They're stem cells that give rise to other blood cells (WBCs and RBCs).

Characterized by:

Any abnormalities of hematopoietic stem cells will give many diseases. ↑ results in cancer, ↓results in anemia.

1. Ability of self renewal
2. Cell differentiation

#Extra



Regulation of Hematopoiesis

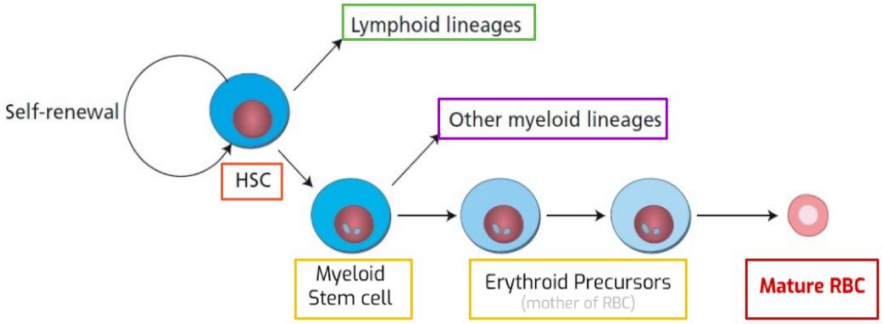
Regulation of hematopoiesis is mediated by **Transcriptional Factors**

Which includes: **Transcriptional Factors:** proteins that are capable of controlling gene expression, regulating the stem cell functions and differentiation

Transcriptional Factors

The controlling factors/triggering factors

- **Erythropoietin** — from kidney
- **GATA1**



- Hematopoiesis started by HSC
- HSC will be divided to lymphoid lineages and myeloid stem cell
- Myeloid SC divided to other myeloid lineages which give WBCs (discussed later) and Erythroid Precursors are found in the bone marrow which give mature RBCs
- Exists and goes to the circulation, results in 4^6 cells.
- All process must be normal to give normal RBCs in function, size and shape

Introduction
Erythropoiesis

Formation of RBCs

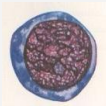
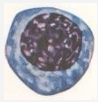
The **bone marrow** is the major site of erythropoiesis it can occur in many site but this is the main site ,with the need of :

1. Folic acid
2. Erythropoietin
3. Iron (Fe2+) Ferrous form
4. Vit B12
5. Amino acid minerals and other regulatory factors

Formation of RBCs started from Erythroblast

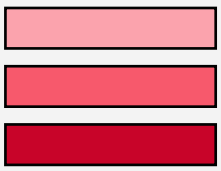
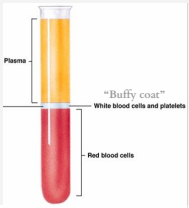
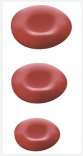
Hb synthesis begins at erythroblast and stops at reticulocyte, but it is highly active at normoblasts **especially intermediate normoblast.** It occurs at all stages of RBC synthesis except in mature erythrocyte, and it's anucleated because the Hb can take place inside the cells.

all process must be normal to give normal RBCs in function , size and shape

	Erythroblast	Basophilic Normoblast	Intermediate Normoblast	Late Normoblast	Reticulocyte	Erythrocyte (The only form which will go to circulation)
Cell						
Hb Synthesis	+	++	+++	++	+	No Hb synthesis here –
Location	Bone marrow					Circulation

Normal CBC ranges

male Dr: important, especially MCV

	Important to know Hb values: Hemoglobin (g/dL) (↑ Hb = Polycythemia, ↓ Hb = Anemia)	Hematocrit (PCV) (%)	Red Cell Count ($\times 10^{12}$)	Mean Cell Volume (MCV) (fL = femtoliters) size of RBCs	Mean Cell Hemoglobin (MCH) (pg = picograms) pigment ratio in RBCs
Male	13.5 – 17.5	40 – 52	4.5 – 6.5	80 – 95	30 – 35
Female	11.5 – 15.5	36 – 48	3.9 – 6.5		
	 Test color of Hb			 Macrocytic Normocytic Microcytic less than 80 (micro) above than 95 (macro)	Normochromic white and red areas equal Hypochromic white area higher Pale in colour

Difference between male and female due to menstrual cycle

Anemia

Definition

- **An** (without) **-aemia** (blood): It is reduction of Hb concentration **below** the normal range for the **age** and **gender**. (disorder in Hemoglobin conc.)
- Leading to decreased O2 carrying capacity of blood and thus O2 availability to tissues (**hypoxia**)

Clinical features:

Presence or absence of clinical feature depends on:

1. **Speed of onset:** Rapidly progressive anemia causes more symptoms than slow onset anemia due to lack of compensatory mechanisms: cardiovascular system, bone marrow (BM) and O2 dissociation curve.
2. **Severity:** Mild anemia → no symptoms usually .
   ☆Hb is **less than 9g/dL** → Symptoms appear
3. **Age:** Elderly tolerate anemia **less** than young patients
   Because they have risk of developing heart failure, and their compensatory mechanism is weaker

Clinical Features:

Related to Anemia

- Weakness & Headache
- **Pallor**
- Dizziness & Lethargy

Related to Compensatory Mechanisms

- Palpitation (tachycardia)
- Angina Especially with preexisting coronary artery disease
- Cardiac failure Due to the fear of HF we must not overlook mild anemia in elderly

How does our body detect anemia? Our body detects it by **hypoxia,** and not through measuring the Hb concentration. When hypoxia is detected, compensatory mechanisms start and a message is sent by erythropoietin to the bone marrow signalling the need for generating more RBCs and hemoglobin.

Classification of Anemia

Classification Based on morphology	Mechanism	Etiology	
		Anemia ☆	Cause
Hypochromic Microcytic Anemia Low MCH small size Low hemoglobin	Disruption or reduction of **Hemoglobin** components	**Sideroblastic anemia**(vampire disease)	Reduction in **Porphyrin**
		Iron def. Anemia	decreased levels of **iron**
		Thalassemia	Reduction in **globin chain**
Normocytic Normochromic Anaemia Low hemoglobin Normal MCV, MCH	Reduction in **RBC** count	**Blood loss** most common cause	Acute bleeding
		Hemolysis RBCs broken in circulation	• Autoimmune • Enzymopathy • Membranopathy • Mechanical artificial valve • Sickle cell anemia
	Disruption of RBCs **production:**	Bone marrow failure	• Chemotherapy • Aplastic anemia shut down of bone marrow • Malignancy
		Anemia of chronic disease	
Macrocytic Anemia High MCV	Disruption of **DNA** synthesis	**Megaloblastic anemia** most common cause:	
		• **Deficiency of vitamin B12 and Folate** • MDS (Myelodysplastic syndrome)	

Sideroblastic anemia Causes:1- genetic (eg, X-linked defect in ALA synthase gene), 2-acquired (myelodysplastic syndromes), and reversible (alcohol is most common; also lead poisoning, vitamin B 6 deficiency, copper deficiency, drugs [eg, isoniazid, linezolid])
Treatment: pyridoxine (B6 , cofactor for ALA synthase).

Thalassemia is of 2 types:
1-α-thalassemia: α-globin gene deletions on chromosome 16 → ↓α-globin synthesis. Normal is αα/αα. Often ↑RBC count, in contrast to iron deficiency anemia
2-β-thalassemia:Point β-thalassemias mutation in splice sites or Kozak consensus sequence (promoter) on chromosome 11→ ↓β-globin synthesis (β+) or absent β-globin synthesis (β0).

Iron Deficiency Anemia

Iron Deficiency Anemia (IDA)

IDA affects mental activity in children

common cause of anemia

- The most common disorder (24%)
- Iron is among the abundant minerals on earth (6%)

Cause:

- excess loss due to hemorrhage period in female
- Iron has limited absorption ability:
  - Only 5-10% of taken iron will be absorbed
  - Inorganic iron can not be absorbed easily.

Team 436: **Why can so little of iron be absorbed?**
Because iron itself is very toxic for the body, and its accumulation due to increased iron absorption for example may lead to hemochromatosis (iron overload disease) which may lead to deficiency of many glands and leads to disease like diabetes.

Causes

1-Chronic blood loss - Major cause (most common) (80% of cases)

- GIT bleeding: peptic ulcer, esophageal varice, hookworm & cancer
- Uterine bleeding most common cause in female
- Hematuria

2-Increased demands

- Immaturity. because it's very toxic
- Growth
- Pregnancy
- EPO Erythropoietin therapy

neonates and infants need to be fed with iron containing milk

3-Malabsorption

- Enteropathy
- Gastrectomy

4-Poor diet

- Rare as the only cause (rule out other causes)

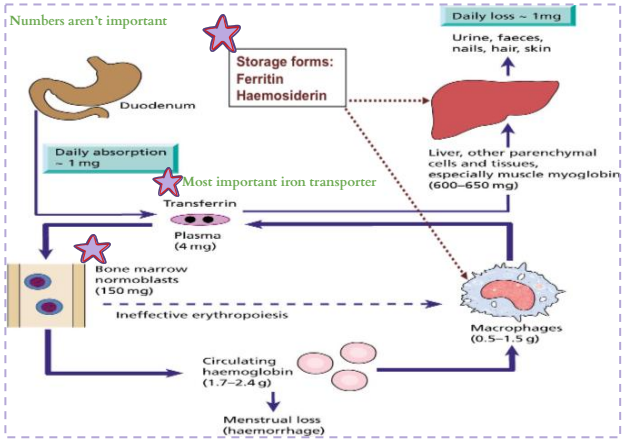
↓iron due to chronic bleeding (eg, GI loss, heavy menstrual bleeding), malnutrition, absorption disorders, GI surgery (eg, gastrectomy), or demand (eg, pregnancy) → **↓final step in heme synthesis.**

Iron Deficiency Anemia

Iron Cycle & Storage:

- Iron **site of absorption**(1mg): Duodenum
- then will take the iron by Iron **carrier protein**: transferrin in plasma (4mg)
- then will take it in bone marrow (factory,need) which is the site of production of RBCs to the normoblasts (150mg)
- then mature RBCs will go to the circulation with the iron
- RBCs can be lost by period in female, from circulation it can go to reticuloendothelial system after half life of RBCs (120 day) will store in macrophage (store area of iron) storge form: Ferritin , haemosiderin when we need the iron it can be broken from the storage form and return to circulation
- some of iron go to the liver store especially in muscle myoglobin
- Can also loss in urine , faeces , nails , hair , skin

Check the video(iron absorption)in the playlist for good understanding :)



Extra, Figure interpretation:

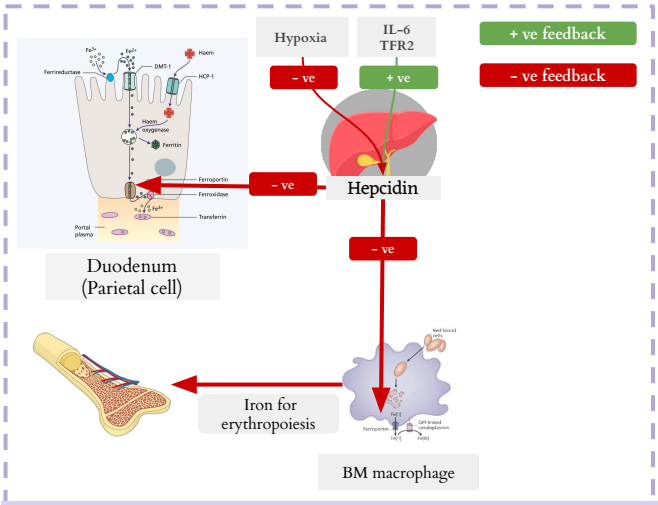
- Greatest amount of iron in the body **is found in the circulation** (1.7 - 2.4 g), and it is reutilized for **hemoglobin synthesis** when RBCs die. Iron is transferred **from macrophages** to **plasma transferrin** and then **to bone marrow** for **erythropoiesis**.
- Iron absorption is normally just sufficient to make up for iron loss. Daily iron absorption (1mg) = Daily iron loss (1mg)

Hepcidin Role in Iron Cycle & Storage:

Iron absorption occur in duodenum in 2 areas: DMT-1 (gate control absorption) , ferroportin.
these areas control by key molecule Hepcidin (keymaster hormone secreted by the liver, control iron status in the body).
iron in food in Fe3+ must convert to Fe2+ and the will enter to the duodenum area. can be stored in ferritin form or enter to circulation transfer by transferrin in the portal plasma to the bone marrow
hepcidin can also control in the store area (macrophage) in RES inhibit or secrete depend on the demand

What is the mechanism behind the positive feedback effect of IL-6?

It is a **protective mechanism** formed by the body during inflammation (IL-6 is an inflammatory cytokine) to prevent microorganisms from utilizing iron in their pathogenesis .



Hypoxia → ↓ Hepcidin release → ↑ Iron absorption

IL-6 or TFR2 → ↑ Hepcidin release → ↓ Iron absorption

Extra, Figure interpretation (Duodenum):

- Iron enters the body in the **ferric form (Fe3+)**. For iron to enter the duodenum cells it must be converted to the **ferrous form(Fe2+)** by the enzyme **ferrireductase**. When the iron is released to the circulation it is released in the **ferric form** by the enzyme **ferroxidase** so, it can be carried in circulation by **transferrin**.
- Ferric ion (Fe3+) = non-absorbable form
- Ferrous ion (Fe2+) = absorbable form

Iron Deficiency Anemia

Iron Absorption

Body iron status

Increased demands → Low iron stores → **High** absorption
(iron deficiency, pregnancy...)

Iron overload → Full iron stores → **Low** absorption

Content and form of dietary iron

- More iron
- Heme iron
- Ferrous iron

} All lead to **more absorption**

Balance between dietary enhancers & inhibitors

Enhancers	Inhibitors
• Meat (Heme iron) • **Fruit (Vit C)** • **Sugar (solubilizing agent)** • **Acids**	• Dairy food (calcium) • High fibers food (phytate) • **Coffee/tea (polyphenols)** • **Anti -acids**

Factors favoring absorption	Factors reducing absorption
1. Heme iron **2. Ferrous Iron (Fe2+)** 3. Acid **4. Iron deficiency** 5. Pregnancy 6. Hemochromatosis 7. Solubilizing agent (sugar)	1. Inorganic iron **2. Ferric iron (Fe3+)** 3. Alkalines 4. Iron overload **5. Tea** شاهي بعد الاكل ❌ 6. Increased hepcidin due infection 7. Precipitating agent (phenol)

Iron Deficiency Anemia

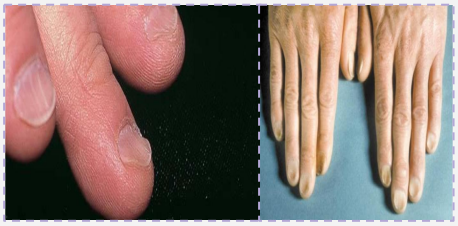
Development of IDA

Signs of Anemia	Normal	Pre-latent	Latent	Iron def. anemia
Stores	Normal	Low	Low	Low
MCV/MCH	Normal	Normal	Low	Low
Hemoglobin	Normal	Normal	Normal	Low

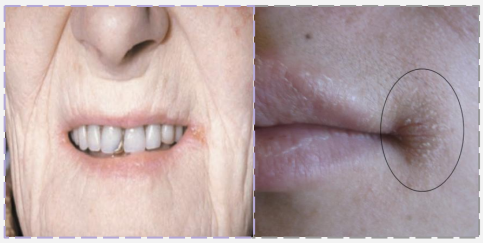
Signs and symptoms of iron def. anemia will not appear until three parameters are affected (Stores, MCV/MCH, Hemoglobin).in the last stage

Signs and Symptoms of IDA

Beside symptoms and signs of anemia (mentioned previously), +/- bleeding patients present with:



Koilonychia
(spoon-shaped nails)
Most specific sign



Angular stomatitis
and/or glottitis
Fissures around the mouth
specific sign

Dysphagia due to pharyngeal web in esophagus
(Plummer-Vinson syndrome)
more sever

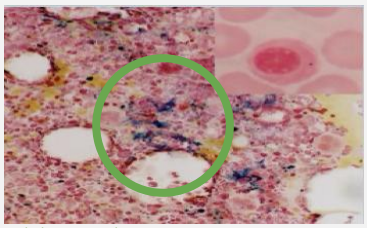
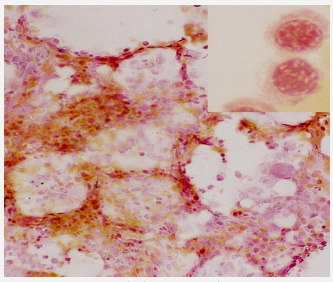
- **Angular stomatitis:** Inflammatory condition causing red, swollen patches in the corners of the mouth
- **Glossitis** (swollen and inflamed tongue)
- **Plummer-Vinson syndrome (PVS)** which is a rare condition characterized by a triad of IDA, dysphagia, and esophageal webs
- **Pharyngeal web:** Protrusion of normal esophageal tissue into the esophagus causing dysphagia

Iron Deficiency Anemia

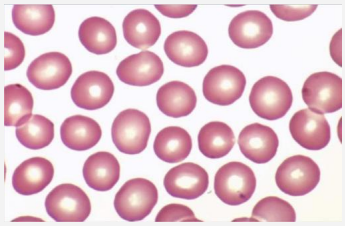
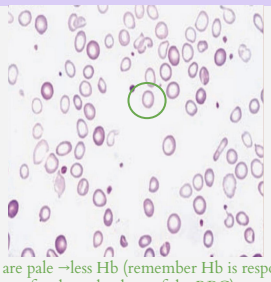
Investigations first investigation after CBC (Blood film)

1- Perl's stain Prussian blue Important to know stain's name

BM iron stain detecting presence of iron, **gold standard** but **invasive** procedure

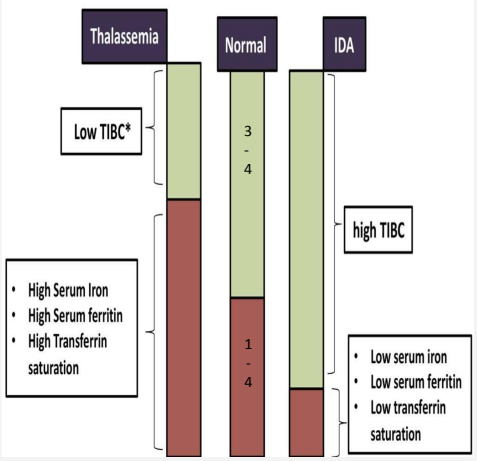
Normal	IDA	
 blue color Normal bone marrow. Stain should be blue with blue dots in erythroids.	 no blue color	**Perl's stain in IDA:** • Reduced or absent iron stores (hemosiderin) • Absent blue dots in Erythroids since there's no iron

2- Morphology of IDA

Normal	IDA	
 Normal microscopy of blood	 1-RBC are pale →less Hb (remember Hb is responsible for the red colour of the RBC) 2-Reduction in RBC count	**microcytic hypochromic anemia** with: When IDA is classified based on morphology, it appears as microcytic hypochromic anemia • Anisocytosis (variation in size) • Poikilocytosis (variation in shape)

3- Iron studies iron profile Blood tests used to evaluate body iron stores or the iron level in blood serum.

	Iron Deficiency Anemia	Thalassemia
TIBC (Total iron binding capacity of transferrin)	↑	↓
Serum iron	↓	↑
Serum ferritin (iron store)	↓	↑
Transferrin saturation	↓	↑



Iron Deficiency Anemia

Treatment

1- Treat the underlying cause	Always start with oral therapy **2- Iron replacement therapy** if the underlying cause not clear	3-Blood transfusion:
	• **Oral**: ferrous sulfate OD(once daily) for 6 months. • **IV**: ferric sucrose OD for 6 months If there was no response (If the patient's oral treatment didn't respond, IV should be given) we also give fibers to prevent constipation	In **severe cases** to improve signs and symptoms

Response to treatment:

Hb should rise 2g/dL every 3 weeks (good response).

- Good response: Rise in Hb level after treatment
- No response: No rise in Hb level after treatment

Prevention

1-Dietary modification:	**Red Meat** is better source than vegetables.
2-Iron supplementation:	For high risk groups (Pregnant women & Children)
3-Food fortification (with ferrous sulfate):	It causes GIT disturbances, staining of teeth and metallic taste. (So It's not a preferable preventative measure).

If there is no response, it could be due to three reasons:

1- You don't treat the underlying cause or diagnose the patient properly
2- Unreported or unnoticeable bleeding (rectal bleeding in colon cancer)
3- The patient is not compliant with the treatment

Anemia of Chronic Disease

Anemia of Chronic Disease Common cause after iron

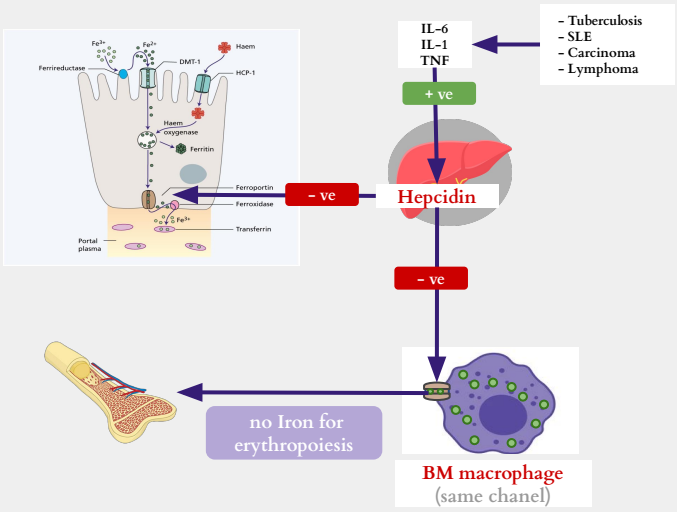
Overview

- Usually characterized by **normochromic normocytic anemia** Caused by **decreased release** of iron from iron stores due to raised serum Hepcidin

associated with:

1. **Malignancy (Most common)**
2. Chronic inflammations
3. Chronic infections including HIV, malaria, TB
4. Tissue necrosis

Pathophysiology

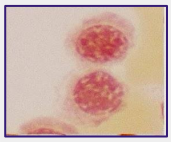


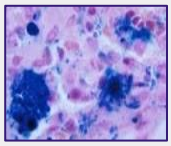
Team 438 Explanation

Chronic diseases like TB, SLE, carcinoma and lymphoma releases a lot of **IL-6, IL-1 and TNF** these are responsible of the high hepcidin levels which is in turn **prevents** the **release of iron** from the stores, so there is NO iron for erythropoiesis.

Work-up and treatment

- Normocytic normochromic in general or mildly microcytic anaemia
- **Low serum iron and TIBC**
- Normal or high serum ferritin (acute phase reactant)
- High hemosiderin in macrophages but **low in normoblasts**





Management

1. **Treat the underlying cause**
2. Iron replacement +/- Erythropoietin (EPO)

Summary

EXTRA

Hemoglobin

- HbA is composed of Heme (Iron binding O2 Fe2+, protoporphyrin ring) and globin chains (α & β) and it's the major type of Hb in Adults.

Hematopoiesis

- Regulation of hematopoiesis is mediated by Transcriptional Factors which includes: Erythropoietin & GATA1.
- Hematopoietic Stem Cells (HSCs) characterized by: **Ability of self renewal & cell differentiation**

Erythropoiesis

- It's major site is the bone marrow
- Regulatory factors needed for erythropoiesis: Folic Acid, Vit.12, Ferrous form iron (Fe+2), erythropoietin, amino acids, minerals and others

Stages of erythropoiesis

Cell	Erythro-blast	Basophilic Normoblast	Intermediate Normoblast	Late Normoblast	Reticulo-cyte	Erythrocyte (RBC) The only form which will go to circulation
Hb Synthesis	+	++	+++	++	+	-

Anemia

It is the reduction of Hb concentration **below** the normal range for the age and gender. **typical value would be:** less than 13.5 g/dL in adult male, less than 11.5 g/dL in adult female, less than 14 g/dL in newborn infant. **MCV: (80-95), MCH: (30-35)**

Classification of anemias

Hypochromic Microcytic (Disruption of Hb)	Normocytic Normochromic (Reduction in RBCs)	Macrocytic (Disruption of DNA synthesis)
-Sideroblastic anemia -Iron def. Anemia - Thalassemia	**Reduction in RBCs count:** **-Blood loss: acute bleeding** **-Hemolysis:** Sickle cell anemia **Distribution of RBCs production:** - Bone marrow failure -Anemia of chronic disease	-Megaloblastic anemia -MDS (Myelodysplastic syndrome)

Iron Deficiency Anemia

Major cause is chronic blood loss. eg: GIT bleeding

Iron metabolism and absorption

Iron is carried by transferrin and stored as ferritin and hemosiderin. Ferroportin is the gate of iron from cell to circulation. Absorption of iron occurs in the duodenum and its controlled by hepcidin through negative feedback of ferroportin:

- Hypoxia → ↓ Hepcidin release → ↑ Iron absorption
- IL-6 or TFR2 → ↑ Hepcidin release → ↓ Iron absorption

Factors Favoring Absorption	Heme iron	Ferrous Iron (Fe2+)	Pregnancy	Acid	Iron deficiency
Factors Reducing Absorption	Inorganic iron	Ferric iron (Fe3+)	Increased hepcidin	Alkaline	Iron overload

Features

Angular stomatitis, koilonychia, dysphagia

Investigations

- Absence of iron in Perl's stain
- Microcytic hypochromic anemia on morphology

Anemia of Chronic Disease

- Characterized by **normochromic normocytic anemia, low serum iron and TIBC, high serum ferritin (acute phase reactant)** (main thing to differentiate between IDA and Anemia of Chronic Disease is Ferritin serum)
- **Caused by** decreased release of iron from iron stores due to raised serum Hepcidin
- Mostly associated with Malignancy
- Managed by **Treat the underlying cause**

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