MED439
KING SAUD UNIVERSITY

Anemia

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.

Dr's notes
Important
Extra notes
** Only in girls slide
** Only in boys slide

Editing file

Revised & Approved
Bassam Alasmari
Rania Almutiri

Hematology Team

Introduction

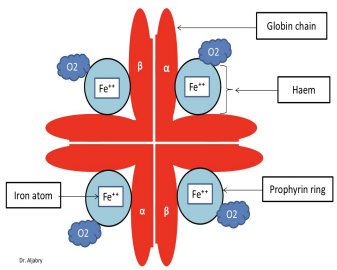
Hemoglobin Function

- RBCs contain hemoglobin, a protein that carries O2 from the lungs to the body's tissues and returns carbon CO2 from the tissues back to the lungs.
- Hemoglobin **maintains** the shape of RBCs and pH of the blood.

Hemoglobin Structure

- There are many types of hemoglobin. HbA is the major hemoglobin found in adults.
- **HbA** is made up of four polypeptide subunits, two alpha (α) subunits and two beta (β) subunits.
- Each hemoglobin molecule has 4 heme groups and can bind to 4 molecules of O2.

Components of <u>one</u> HbA			
Heme (Non protein)		Globin chain (protein)	
Iron binding O2 (Ferrous state, Fe2+)	Protoporphyrin ring	α chain	β chain



Quick Recap - To be discussed later...

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

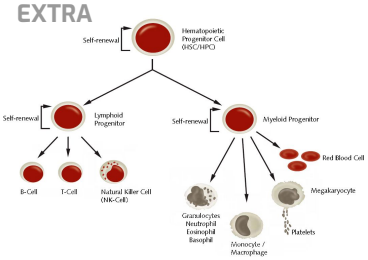
Hematopoiesis

Hematopoietic Stem Cells (HSCs)

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

- Ability of **self renewal** and **cell differentiation** to all functional blood cells

EXTRA



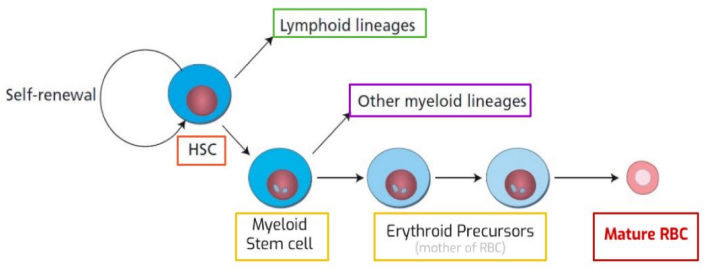
Hematopoiesis

- **Definition**: is the production of all of the cellular components of blood and blood plasma through hematopoietic stem cells.
- HSCs have to be **normal** to have a normal hematopoiesis process and produce normal RBCs,
- Hematopoiesis is a **tightly regulated** process as it maintains the blood according to the body's needs.
- Any abnormalities of hematopoietic stem cells will give many diseases. ↑ results in cancer, ↓results in anemia.

Regulation of Hematopoiesis - Transcriptional Factors

- In order for the body to regulate hematopoiesis we have **transcriptional factors**
- They are proteins that are capable of controlling gene expression, regulating the stem cell functions and differentiation.
- **Transcription factors controlling hematopoiesis include:**
  - **Erythropoietin** (90% is synthesized in kidney, 10% is synthesized in liver)
  - GATA1

Doctors explanation of the following figure:



- HSC will be divided to lymphoid and myeloid cell line
- Give rise to T, B lymphocytes
- Give rise to white blood cells (neutrophils, basophils, monocytes...) and platelets
- Myeloid SC & Erythroid Precursors are found in the bone marrow
- Exists and goes to the circulation

Introduction

Erythropoiesis

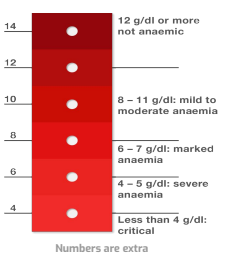
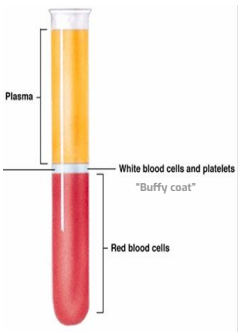
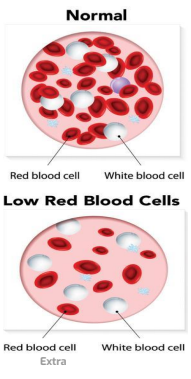
The major site of erythropoiesis is the **bone marrow** with the need of other regulatory factors:

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

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.

	Erythroblast	Basophilic Normoblast	Intermediate Normoblast	Late Normoblast	Reticulocyte	Erythrocyte
Cell					 Found in circulation only when bone marrow is under stress or in severe anemia	 No nucleus just RNA and enzymes
Hb Synthesis	+	++	**+++** (high amount of Hb synthesis)	++	+	- (No Hb synthesis)
Location	Bone marrow				Circulation	

Normal CBC Ranges

	Hemoglobin (g/dL)	Hematocrit (PCV) (%)	Red Cell Count ($*10^{12}$)	Mean Cell Volume (MCV) (fL)	Mean Cell Hemoglobin (MCH) (pg)
Male	13.5 - 17.5	40 - 52	4.5 - 6.5	80 - 95	30 - 35
Female	11.5 - 15.5	36 - 48	3.9 - 5.6		
	 ↑ Hb = Polycythemia ↓ Hb = Anemia			 Macrocytic Normocytic Microcytic ↑ MCV = Macrocytic cell ↓ MCV = Microcytic cell	Normochromic  Hypochromic Low hemoglobin.  ↓ MCH = Hypochromic cell *We don't have hyperchromic cells as the cells will divide immediately once we have enough number of hemoglobin molecules.

Anemia

Pathoma

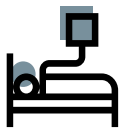
Definition

- An (without) -aemia (blood): It is reduction of Hb concentration **below** the normal range for the **age** and **gender**, Neonate born with 13 g/dL of hemoglobin is anemic, whereas for adults this value is considered normal.
- Leading to decreased O2 carrying capacity of blood and thus O2 availability to tissues (hypoxia)

Clinical Features

Related to Anemia

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



Related to Compensatory Mechanisms

- Palpitation (tachycardia)
- Angina, especially with preexisting coronary artery disease
- Cardiac failure
- These features are seen in severe conditions where Hb is less than 6g/dL

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), O2 dissociation curve (shift to the right)

2. **Severity**
   - Mild anemia: Usually no symptoms
   - Symptoms appear if Hb is **less than 9g/dL**

3. **Age**
   Elderly tolerate anemia less than young patients because the compensatory mechanisms are not fit like in the young patients .

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.

Anemia

Pathoma

★ Classification (Based on Morphology)

Anemia can be classified based on the size of the red blood cells (MCV interpretation) and amount of hemoglobin in each cell (MCH interpretation).

	Hypochromic Microcytic Anemia	Normocytic Normochromic Anemia	Macrocytic Anemia
MCV	<80	80-100	>100
Mechanism	Disruption or reduction of Hemoglobin components	Reduction in RBC count	Disruption of DNA synthesis

★★★ **Etiology**	-Any cause that leads to reduction of hemoglobin content will produce hypochromic microcytic anemia
	-What are the possible causes?
	Thalassemia, iron deficiency sideroblastic anemia
	• **Sideroblastic anemia**→ caused by Reduction in Porphyrin
	• **Iron def. Anemia**→ due to decreased levels of iron
	• **Thalassemia** → Reduction in globin chain (α or β)
		• Blood loss (most common)→ Acute bleeding
		• Hemolysis →
		  ○ Autoimmune
		  ○ Enzymopathy
		  ○ Membranopathy
		  ○ Mechanical
		  ○ Sickle cell anemia
		• Disruption of RBCs production:
		  ○ Bone marrow failure→ Chemotherapy, Aplastic anemia, Malignancy
		  ○ **Anemia of chronic disease**
			• **Megaloblastic anemia** (most common)→ caused by **Def. of vitamin B12 and Folate**
			• MDS (Myelodysplastic syndrome)

Iron Deficiency Anemia (IDA)

Pathoma (skip to 6:00 for IDA) Osmosis

- The **most common disorder** (24%)
- Iron is among the abundant minerals on earth (6%)
- The body has no method to get rid of iron, so excessive loss can only be due to hemorrhage which can be a cause of anemia
- Iron has limited absorption ability:
  - Only 5-10% of taken iron will be absorbed
  - Inorganic iron can not be absorbed easily.
- IDA affects mental activity in children

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

01 Chronic blood loss - Major cause (80% of cases)

- **GIT bleeding**: peptic ulcer, esophageal varice, hookworm & cancer
- Uterine bleeding
- Hematuria

Team 436: During hemorrhage (bleeding), iron stores are depleted due to increased iron demand for hematopoiesis.

02 Increased demands

- Immaturity (neonates and infants need to be fed with iron containing milk)
- Growth
- Pregnancy
- Erythropoietin therapy

03 Malabsorption:

- Enteropathy
- Gastrectomy

Team 435: Malabsorption occurs due to **dec. acidity**, which is needed for ferrous absorption.

04 Poor diet

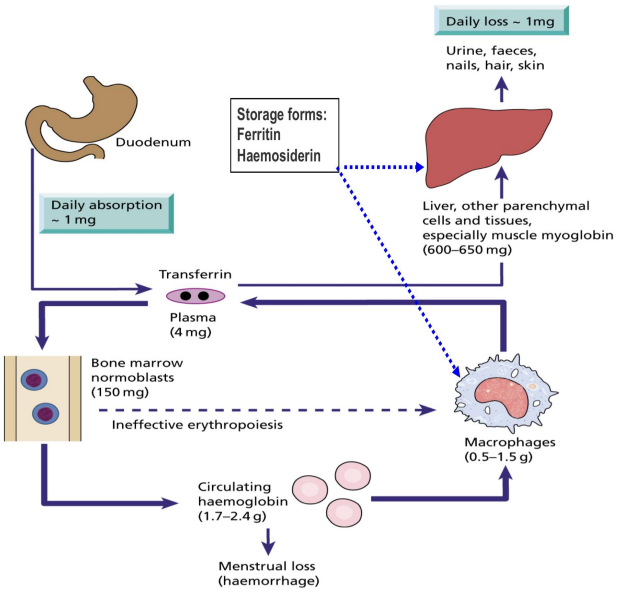
Rare as the only cause (rule out other causes)

Iron Deficiency Anemia (IDA)

Armando

Iron Cycle & Storage

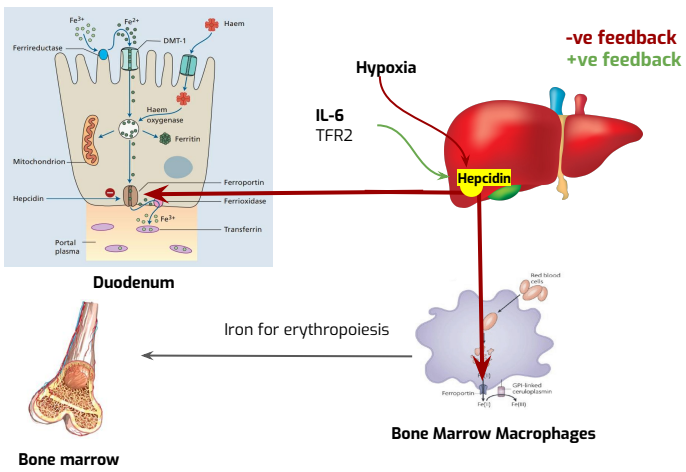
This whole slide was explained using pics only from original slides



- **Iron site of absorption:** Duodenum
- **Iron carrier protein:** transferrin, each transferrin carries 2 molecules of ferric iron
- **Iron storage sites:** Iron is carried by transferrin to liver, muscle myoglobin and macrophages for storage
- **Iron is stored in in the form of:** ferritin and hemosiderin

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)



Interpretation of Duodenum Figure:

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

Hepcidin

- It is a hormone secreted by the liver.
- It is the master that controls iron absorption through **negative feedback** of ferroportin.
- Hepcidin hormone is inversely proportional to iron absorption.
- Function: Inhibits the function of ferroportin transporter in **small intestine** (duodenum) and **macrophage**, to inhibit the release of iron to circulation (absorption process).

Hypoxia → ↓ Hepcidin release → ↑ Iron absorption

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

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

Iron Deficiency Anemia (IDA)

Iron Absorption

1 Body iron status

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

Iron overload → Full iron stores → Low absorption

2 Content and form of dietary iron

- More iron
- Heme iron
- Ferrous iron

} **All lead to more absorption**

3 Balance between dietary enhancers & inhibitors

Enhancers

- Meat (Heme iron)
- **Fruit (Vit C)**
- **Sugar (solubilizing agent)**
- Acids

Inhibitors

- Dairy food (calcium)
- High fibers food (phytate)
- **Coffee/tea (polyphenoles)**
- Anti -acids

Factors Affecting Absorption

★★★

Favoring Absorption	Reducing Absorption
1. Heme iron	1. Inorganic iron
2. Ferrous Iron (Fe2+)	2. Ferric iron (Fe3+)
3. Acid	3. Alkalines
4. Iron deficiency	4. Iron overload
5. Pregnancy	5. Tea
6. Hemochromatosis	6. Increased hepcidin
7. Solubilizing agent (sugar)	7. Precipitating agent (phenol)

Iron Deficiency Anemia (IDA)

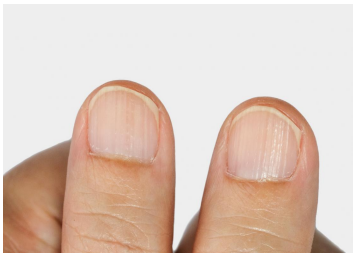
Development of IDA

	Normal	Pre-latent	Latent	**Iron def. anemia
Stores	Normal	Low	Low	Low or absent
MCV/MCH	Normal	Normal	Low	Low
Hemoglobin	Normal	Normal	Normal	Low

** Signs and symptoms of anemia will not appear until three parameters are affected (Stores, MCV/MCH, Hemoglobin).

Signs and Symptoms

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



Koilonychia
(spoon-shaped nails)

Angular stomatitis
and/or glottitis
Fissures around the mouth

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

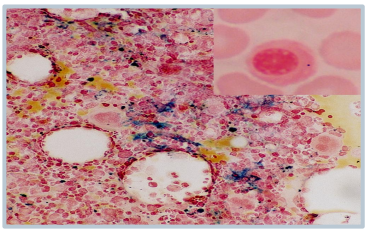
- Angular stomatitis: Inflammatory condition causing red, swollen patches in the corners of the mouth
- Glossitis (swollen and inflamed tongue)
- Plummer-Vinson syndrome (PVS) which is a rare condition characterized by a triad of IDA, dysphagia, and esophageal webs
- Pharyngeal web: Protrusion of normal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

Iron Deficiency Anemia (IDA)

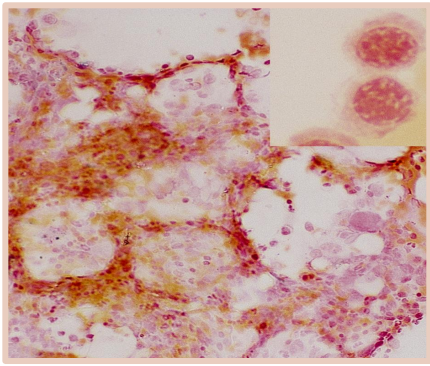
Investigations

01 (Perl's Prussain blue stain):

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



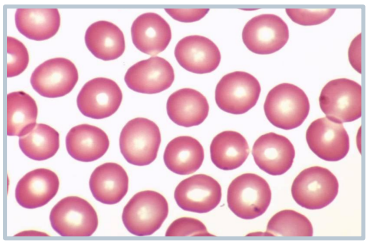
Normal bone marrow. Stain should be blue with blue dots in erythroids



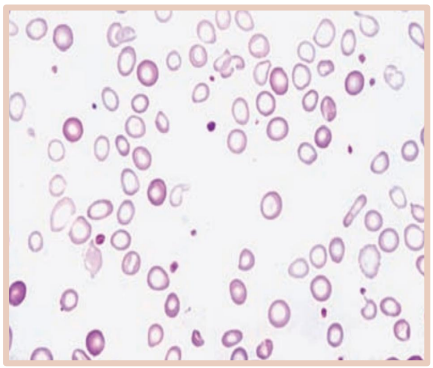
Perl's stain in IDA:

- Reduced or absent iron stores (hemosiderin)
- Absent blue dots in erythroids since there's no iron.

02 Morphology of IDA



Normal microscopy of blood



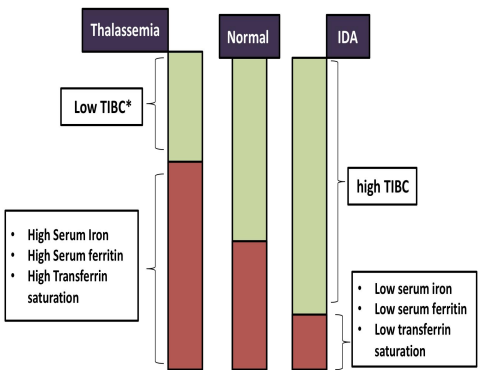
When IDA is classified based on morphology, it appears as **microcytic hypochromic anemia** with:

- **Anisocytosis (variation in size)**
- **Poikilocytosis (variation in shape)**

03 Iron studies:

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)	↑ The body produces more transferrin so it can bind to more iron as compensatory mechanism of iron def.	↓
Serum iron	↓	↑
Serum ferritin (iron store)	↓	↑
Transferrin saturation	↓	↑



In case of thalassemia, everything is high except for TIBC its low (Thalassemia will be discussed in later lectures). The problem here is not reduction of iron, but the reduction of globin chain. So there will be a lot of iron without any function.

Iron Deficiency Anemia (IDA)

Treatment

Treat the underlying cause

Blood transfusion: In severe cases to improve signs and symptoms

Iron replacement therapy:

- Oral: ferrous sulfate OD for 6 months.
- IV: ferric sucrose OD for 6 months.
- If the patient's oral treatment didn't respond, IV should be given

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:**
   Meat is a better source than vegetables.

2. **Iron supplementation**
   For high risk groups like pregnant woman children

3. **Food fortification (with ferrous sulfate)**
   It's not a preferable preventative measure as it causes GIT disturbances, staining of teeth and metallic taste.

What is food fortification?

- The process of adding micronutrients to food to improve dietary deficiencies
- It is so known as **food enrichment,**

Anemia of Chronic Disease

Khan Academy

Overview

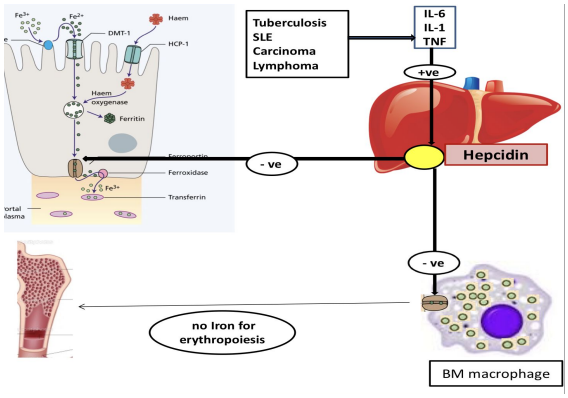
*MCQ

- Usually characterized by **normochromic normocytic anemia**
- **Caused by** decreased release of iron from iron stores due to raised serum Hepcidin unlike in iron deficiency anemia, iron is there in its stores and abundant but the problem is with the release from its storage sites, absorption is not affected (normal)

Anemia of chronic disease is associated with:

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

Pathophysiology

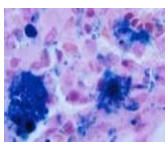


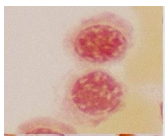
Team 438 Explanation

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.

Investigation

- Normocytic normochromic 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

Treat the underlying cause to prevent further Hepcidin activation

Iron replacement +/- Erythropoietin (EPO)

Summary

Hemoglobin

- A protein carrying O2 from lungs to tissues, returns CO2 from tissues back to the lung.
- **HbA** is composed of Heme (Iron binding O2 Fe2+, protoporphyrin ring) and globin chains (α & β)

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	Erythroblast	Basophilic Normoblast	Intermediate Normoblast	Late Normoblast	Reticulocyte	Erythrocyte (RBC)
Hb Synthesis	+	++	**+++**	++	+	-

Anemia

Reduction of Hb concentration **below** the normal range

Clinical Features

Weakness, headache, pallor, lethargy, dizziness

Classification of anemias (based on MCV & MCH)

Hypochromic Microcytic (Disruption of Hb)	Normocytic Normochromic (Reduction in RBCs)	Macrocytic (Disruption of DNA synthesis)
• Sideroblastic anemia • Iron def. Anemia • Thalassemia	• Sickle cell anemia • **Anemia of chronic disease**	Megaloblastic anemia

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+) • Acid • Iron deficiency	• Pregnancy • Hemochromatosis • Solubilizing agent (sugar)
Factors Reducing Absorption	• Inorganic iron • Ferric iron (Fe3+) • Alkalines • Iron overload	• Tea • Increased hepcidin • Precipitating agent (phenol)

Clinical Features

Angular stomatitis, **koilonychia,** dysphagia

Investigations

- Presence 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**
- **Caused by** decreased release of iron from iron stores due to raised serum Hepcidin
- Mostly associated with Malignancy
- Managed by Treat the underlying cause to prevent further Hepcidin activation

Quiz

Q1) Which ONE of the following is a cause of macrocytic anemia ?							
A	Acute blood loss	B	Myelodysplastic syndrome	C	Chronic disease	D	Sideroblastic anemia
Q2) Which of the following is anemia due to chronic disease ?							
A	Normocytic	B	Microcytic	C	Hypochromic	D	Macrocytic
Q3) Which of the following cell lines differentiation responsible for Hematopoiesis following right after Hematopoietic stem cells?							
A	Reticulocyte	B	Erythrocyte	C	Myeloid stem cells	D	Erythroblast
Q4) Which Clinical Feature is related to compensatory mechanism?							
A	Palpitation	B	Pallor	C	Lethargy	D	Weakness
Q5) Which of the following is true regarding Anemia of chronic disease?							
A	Caused by iron deficiency	B	Decreased serum Hepcidin	C	Associated with Malignancy	D	Treated with oral Ferrous Sulfate tablets
Q6) What is the percentage of absorbed iron in IDA patients ?							
A	5-10%	B	1-5%	C	15-25%	D	25-35%
Q7) which of the following factors increase iron absorption?							
A	High Hepcidin	B	Alkalines	C	Tea	D	Heam iron
Q8) which of the following is the most significant factor in controlling iron absorption?							
A	IL6	B	Ferroportin	C	Ferrireductase	D	Erythropoiesis
Q9) which of the following is NOT common symptom in IDA patients?							
A	Koilonychia	B	Inflammatory bowel disease	C	Angular stomatitis	D	Dysphagia
Q10) In iron replacement therapy, what is the optimal increasing range of Hb?							
A	3g/dL every 2 weeks	B	2g/dL every 3 weeks	C	1g/dL every 3 weeks	D	Non of the above

Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
B	A	C	A	C	A	D	B	B	B

Leaders

Sarah Alobaid Sarah Alqahtani Albara Aldawoud

Organizer

Sarah Alaidarous

Members

Shayma Alghanoum Abdulaziz Alkraida

Note Takers

Shaden Alobaid Faisal Alshehri

Summary

Sarah Alaidarous

Feel free to contact us :
Hematologyteam439@gmail.com