Medicine
TEAM 437

MED437
KING SAUD UNIVERSITY

Anaemia

Objectives :

1. Know how to read a CBC (complete blood count)
2. Describe an approach to common causes of anemia
3. Describe the common terminologies
4. Brief overview of clinical presentation

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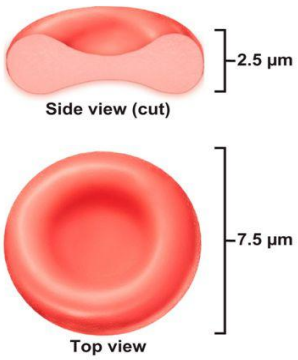
Resources :

- 437 slides | Not Same as 436's slides
- Teamwork 436
- Doctor notes | Dr.Musa AlZahrani & Dr.Farjah AlQahtani

Introduction:

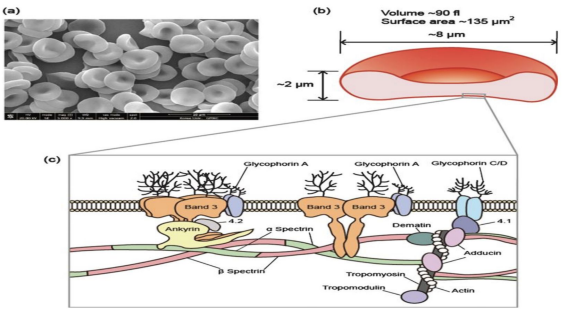
RBC

- Main function is to carry oxygen. The symptoms will results due to reduce Hgb → reduce the delivery of oxygen to our tisse
- Biconcave disks.
- Essentially bags of hemoglobin; few organelles.
- Anucleate (no nucleus).
- Outnumber WBC 1000:1
- Contain the plasma membrane protein spectrin and other proteins.
- Major factor contributing to blood viscosity.



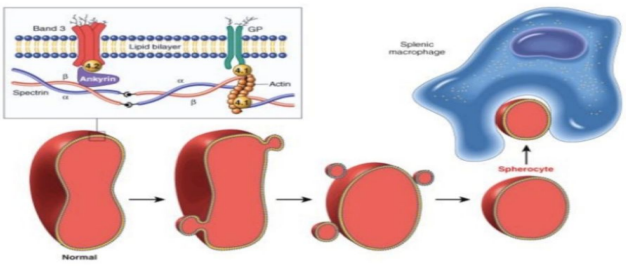
What keeps RBC biconcave? Not imp

- The cytoskeleton, proteins that keeps the RBC in normal shape.
- Abnormality in one of them → abnormal shape

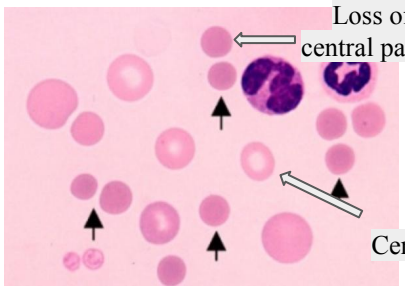


Terminology:

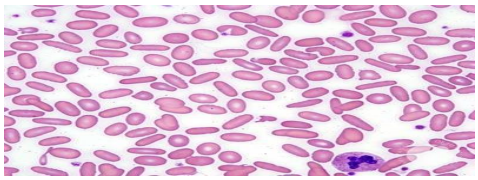
❖ **Spherocytosis:** (sphere-shaped RBC): sloss of Cytoskeletal proteins → Blebs on the surface → Destroyed by splenic macrophages . On peripheral smear (loss of central pallor).



Schematic representation of the red cell membrane cytoskeleton and alterations leading to spherocytosis and hemolysis

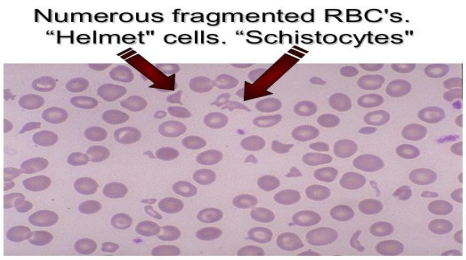


Elliptocytosis: also known as ovalocytosis



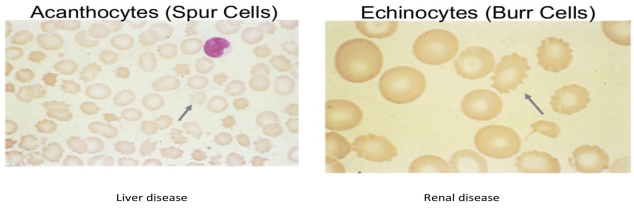
- A hereditary rare blood disorder
- The patient will has anemia and hemolysis

Schistocytes (Helmet cells)



- Fragmented RBCs, demarcated by two sharp Ends.
- It's very alarming bc it could indicate that the patient is suffering from Disseminated Intravascular Coagulation (DIC) or autoimmune hemolytic anemia
- Most imp cause is microangiopathic hemolytic anemia (MAHA) caused by thrombotic thrombocytopenic purpura (TTP) → MEDICAL EMERGENCY.

Spur and Burr cells



- Indicate systemic diseases such as liver or renal diseases

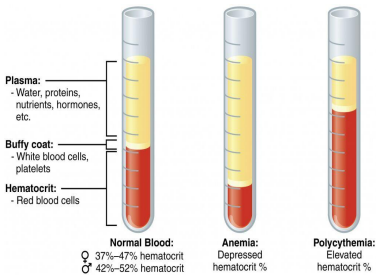
MCV

The **mean corpuscular volume**, or **mean cell volume** (**MCV**)

- Is the average size of a patient's RBCs.
- Is a measure of the average volume of a red blood corpuscle (or RBC).
- It is calculated from the distribution of individual RBC volumes.

Hematocrit

- It's the percentage of PRBC to the total volume of blood sample
- Low in anemia & high in polycythemia
- Automated hematocrit (%) is calculated by multiplying the MCV by the RBC number
- Hematocrit = MCV (10-15 L) × red blood cells (1012/L) × 100.



MCH

The **mean corpuscular hemoglobin (MCH)**

- The average Hb content of a patient's RBCs.
- Is expressed in picograms (10-12 g).
- The MCH is calculated by dividing hemoglobin (g/L) by red blood cell count (1012/L).

❖ MCHC

I look at it only when I suspect spherocytosis

The MCH concentration (MCHC)

- Is the average Hb concentration in each RBC.
- Is expressed in grams of hemoglobin per deciliter of packed RBCs.
- The MCHC is calculated by dividing the hemoglobin concentration (g/ dL) by the hematocrit (%) × 100.

❖ Red blood cell distribution width (RDW)

- The coefficient of **variation** of RBC size (anisocytosis).
- It is used in the **evaluation** of anemia.
- More frequently elevated nutritional deficiencies
- In microcytic anemias: more frequently elevated with **iron deficiency anemia** than to thalassemia or anemia of chronic disease
- In macrocytic anemias: more frequently elevated due to vitamin B12 or folate deficiency than to liver disease, hypothyroidism. = MOSTLY ELEVATED WITH NUTRITIONAL DEFICIENCIES.
- Myelodysplastic syndromes (lead to bone marrow failure), or RBC transfusions to pts with low/high MCV can produce a dimorphic RBC pattern with a high RDW value.
- If all RBCs are large, or all are small, RDW will be normal or even reduced (because although they are abnormal, there is no variation between them).

Complete Blood Count:

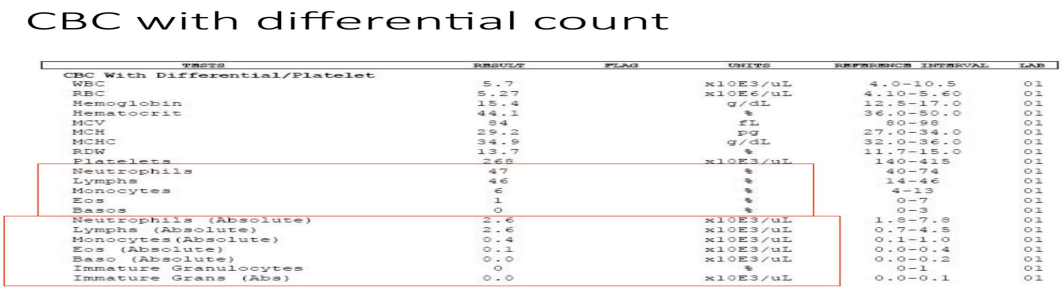
CBC without differential:

CBC

Component Results

Component	Your Value	Standard Range	Units
WBC COUNT	6.7	4.5 - 11.0	K/UL
RBC COUNT	4.51	3.50 - 5.50	MIL/UL
HEMOGLOBIN	14.1	12.0 - 15.0	G/DL
HEMATOCRIT	42.3	36.0 - 48.0	%
MCV	93.7	79.0 - 101.0	FL
MCH	31.2	25.0 - 35.0	PG
MCHC	33.3	31.0 - 37.0	%
RDW-CV	12.4	11.0 - 16.0	FL
PLATELET COUNT	221	150 - 420	K/UL
MPV	9.8	7 - 10	FL

CBC with differential:



CBC with differential count

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
CBC With Differential/Platelet					
WBC	5.7		x10E3/uL	4.0-10.5	01
RBC	5.27		x10E6/uL	4.10-5.60	01
Hemoglobin	15.4		g/dL	12.5-17.0	01
Hematocrit	44.1		%	36.0-50.0	01
MCV	84		fL	80-98	01
MCH	29.2		pg	27.0-34.0	01
MCHC	34.9		g/dL	32.0-36.0	01
RDW	13.7		%	11.7-15.0	01
Platelets	268		x10E3/uL	140-415	01
Neutrophils	47		%	40-74	01
Lymphs	46		%	14-46	01
Monocytes	6		%	4-13	01
Eos	1		%	0-7	01
Basos	0		%	0-3	01
Neutrophils (Absolute)	2.6		x10E3/uL	1.8-7.8	01
Lymphs (Absolute)	2.6		x10E3/uL	0.7-4.5	01
Monocytes(Absolute)	0.4		x10E3/uL	0.1-1.0	01
Eos (Absolute)	0.1		x10E3/uL	0.0-0.4	01
Baso (Absolute)	0.0		x10E3/uL	0.0-0.2	01
Immature Granulocytes	0		%	0-1	01
Immature Grans (Abs)	0.0		x10E3/uL	0.0-0.1	01

Leukocytosis? Which cell line?

- Neutrophilia: Acute: bacterial infection, steroids. Chronic: Chronic myeloid leukemia (CML)
- Lymphocytosis: Acute: viral infections. Chronic: chronic lymphocytic leukemia
- Monocytosis: Fungal infection, TB
- Eosinophilia: allergic conditions, parasite, autoimmune diseases and eosinophilic leukemia
- Basophilia: very rare, CML

Leukopenia? Which cell line?

Neutropenia:

- Mild: Absolute neutrophilic count (ANC): **1.5 - 1** Risk of infection is not increased, no need to investigate.
- Moderate: ANC: **1 - 0.5** Risk of infection is not increased, but need to investigate.
- Severe: ANC: **< 0.5** Risk of infection is increased, must investigate.

WBC	**Low:** Leukopenia /**High:** Leukocytosis
RBC	Measures the absolute RBC count: 1-**Low** 2-**Normal** 3-**High**
HB	**Low:** Anemia if the hematocrit is severely low it means that the patient will have hemolysis and bleeding **High**: Polycythemia
Hematocrit	
MCV	**Low**: Microcytic/ **Normal:** Normocytic/ **High:** Macrocytic
MCH	**Low:** Hypochromic/ **Normal:** Normochromic
MCHC	**High:** Hereditary spherocytosis
RDW-CV	**Normal/Low:** Low or no variation in sizes **High:** High variation in RBC sizes(Anisocytosis)

Anemia:

- Anemia is defined as a reduction of red cell mass, measured by Hct or Hb concentration
- WHO criteria defines anemia as hemoglobin level lower than 12 g/dL in women and 13 g/dL in men
- But: **The reference values for red cells ,Hb or Hct may differ according to:**

  ○ sex/age, race, altitude, socioeconomic changes, study/reference

- When red cell mass decreases, several compensatory mechanisms maintain O2 delivery to the tissues and delay the appearance of symptoms :

  A. Increased cardiac output (heart rate and stroke volume) → may cause high output heart failure over time (HFpEF).

  B. Increased O2 extraction ratio from Hb.

  C. Rightward shift of the oxyhemoglobin curve (increased 2,3-diphosphoglycerate [2,3-DPG]) which will result in reduced Hb-O2 affinity.

  D. Expansion of plasma volume

  E. Tachycardia(because the brain sends message to the heart to pump more oxygenated blood to the brain) and hyperventilation.

❖ **blood transfusion is not recommended unless:**

◇ The Hb concentration is <7 g/dL

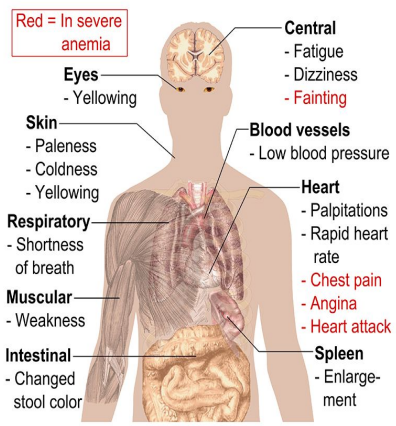
◇ The patient requires increased oxygen-carrying capacity (cardiopulmonary disease or CAD).

◇ <10 g/dL if he has comorbidities like HF!

Clinical features:

The symptoms and findings of anemia concern many different systems/organs due to the widespread nature of **hypoxia**.

- Headache.
- Fatigue, confusion, decreased mental acuity.
- Diarrhea, nausea, vague abdominal discomfort.
- Dyspnea on exertion.
- Pallor of skin or mucous membranes(best noted in conjunctivita), hair loss.
- Hypotension, tachycardia and palpitations.
- **Signs of the underlying cause** orthostatic lightheadedness, syncope or hypotension if acute bleeding; jaundice if hemolytic anemia; blood in stool if GI bleeding.



Approach to anemia

- To start your approach with any case of anemia you need to look at three CBC parameters and one additional test.
- **The 3 CBC parameters are:** (look at them in the following order)
    - The hemoglobin (Hb)
    - MCV to see whether it is microcytic, macrocytic or normocytic
    - Reticulocyte count (retic count).
- And the additional required test is the peripheral blood smear. Looking for spherocytosis, schistocytes and elliptocytosis

With the use of these 3 parameters your approach will be divided into 4 categories:

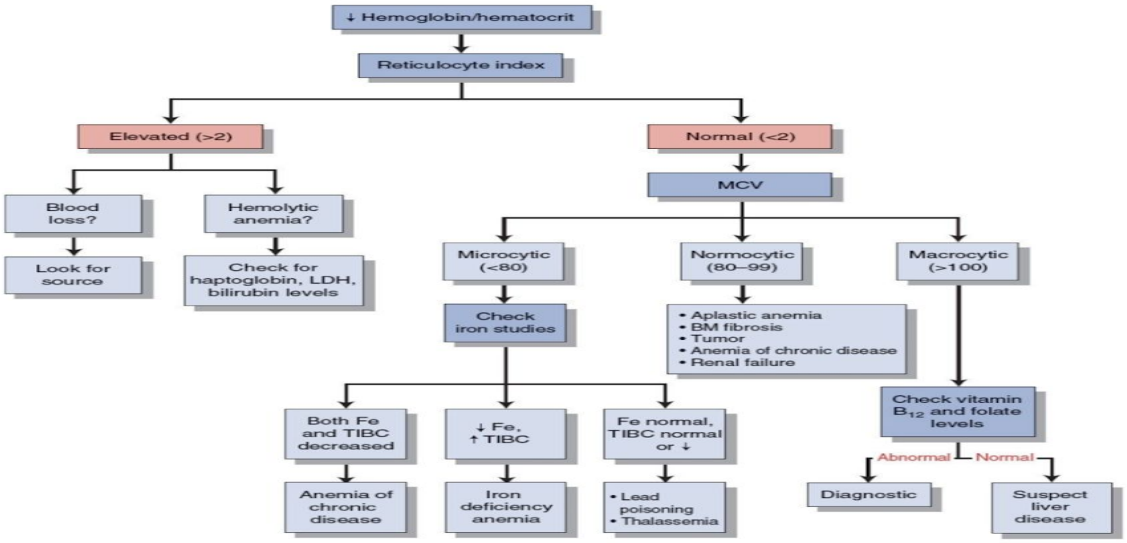
1. **Low MCV** (MCV < 80 fL), also called **microcytic anemia.**
2. **Normal MCV** (MCV 80-100 fL) with **low retic count**, also called **normocytic anemia** with **inappropriately low bone marrow response**.
3. **Normal MCV** (MCV 80-100 fL) with **high retic count**, also called **normocytic anemia with appropriate marrow response.**
4. **High MCV** (MCV >100 fL), also called **macrocytic anemia.**

Reticulocyte Count

- Retic count can be reported as an absolute number or as a percentage.
- It is an important initial test in evaluating anemia because it indicates whether effective erythropoiesis is occuring in the bone marrow.
- A normal retic count/ percentage in the absence of anemia is:
    - **100 or 1%,** respectively.
- When someone with a healthy bone marrow (BM) develops anemia, the BM will automatically compensate for the anemia with production of more young red blood cells (reticulocytes) in anemic pt with low or normal reticulocyte that's mean the problem in the bone marrow itself !
- Thus the retic count will increase and can go up to 1000 or 10% in some severe cases.
- Therefore, a patient with anemia and a healthy bone marrow should have an appropriately elevated retic count.
- In anemia: High retic count indicates healthy bone marrow // Low indicates diseased bone marrow.

❖ A reticulocyte index >2% implies the BM is responding to increased RBC requirements.

❖ A reticulocyte index <2% implies inadequate RBC production by th BM.



DDx of anemia:

MCV <80 fL (TAILS)	MCV N, low retic count	MCV N, high retic count	MCV >100 fL
1) Thalassemia most common 2) **A**nemia of chronic diseases (inflammation) 3) **I**ron deficiency most common 4) **L**ead poisoning 5) **S**ideroblastic anemia very rare	**1) Bone marrow failure:** - Aplastic anemia: virally induced the patient will have flu → after 5 days they will become severely anemic and thrombocytopenic 2) **BM suppression**: - Toxins, sepsis e.g. chernobyl and hiroshima disasters - herbal medication is one of the most important things to ask your patient about. - Organ failure: renal failure, liver failure, adrenal insufficiency - Chronic inflammation - Chronic diseases 3) **BM infiltration:** could be caused by anything; malignant, infection or drugs - Lymphoma, leukemia - Metastatic solid tumors - Granulomatous disease (e.g. TB) - Leishmania - Antipsychotic, antidepressants, and anticonvulsive drugs	The bone marrow is trying to respond to the peripheral needs → release premature RBCs to the circulation the count usually is 1-2 if more it means that the patient is trying to survive 1) Bleeding 2) Hemolysis 3) Treated nutritional deficiency These are the only anemic conditions that cause normal MCV with high reticulocytes	1) **Megaloblastic:** (impaired nucleic acid metabolism): - B12 deficiency - Folate deficiency - Drugs: such as methotrexate changes the metabolism in the RBCs 2) **Non megaloblastic**: - Liver disease - Alcohol - Myelodysplasia - Thyroid disease

Microcytic Anemia

Iron deficiency anemia:

Video

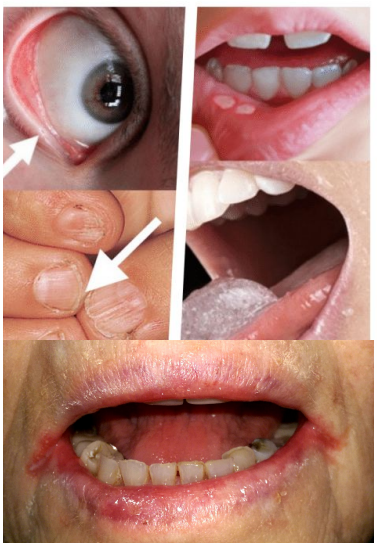
Most common cause of anemia worldwide.

❖ Causes:

1. **Blood loss :** Most common cause of iron deficiency anemia in adults.
   - More common in **female: heavy menses**
   - In **males and post-menopausal women always investigate for GI causes**: occult bleeding, colon cancer. As a result of occult gastric or colorectal malignancy, gastritis and peptic ulceration (GI blood loss may be exacerbated by the chronic use of aspirin or NSAIDs), inflammatory bowel disease, diverticulitis, polyps and angiodysplastic lesions. hookworm and schistosomiasis are common causes in endemic countries.
2. **Malabsorption:**
   - malabsorption, celiac disease etc.
   - Iron is absorbed in the upper **small intestine** > hence can be affected by celiac disease.
   - Gastric acid is required to release iron from food and helps to keep iron in the soluble ferrous state. Achlorhydria in the elderly or that due to drugs such as PPI may contribute to the lack of iron availability from the diet.
3. **Dietary deficiency/increased iron requirements:** a rare cause
4. **Resistance iron deficiency anemia:**

❖ Clinical features:

- Glossitis and Angular stomatitis (in severe deficiency)
- **Pica (pagophagia):** Desire to eat mud or ice. (in severe deficiency)
- koilonychia.
- Pallor.
- Fatigue.
- Generalized weakness
- dyspnea on exertion.
- Orthostatic lightheadedness.
- Hypotension if acute.
- Tachycardia



❖ Diagnosis:

1. **Iron studies:**
   a. Decreased serum ferritin (most specific)
   b. Decreased serum iron (Fe)
   c. Decreased transferrin saturation (TSAT): TSAT< 20% indicates iron deficiency, a TSAT > 50% may indicate iron overload.

   d. Increased total iron binding capacity(TIBC): is a measure of all the proteins in the blood that are available to bind with iron (including transferrin). we do both iron and TIBC test To differentiate between IDA and anemia of chronic diseases.

- Transferrin: is the main transport protein for iron: (Increased in IDA) When iron stores (ferritin) are low, transferrin levels increase and vice versa.

2. **Peripheral blood smear**-reveals microcytic, hypochromic RBCs.
3. **Bone marrow biopsy—**reveals absence of stainable iron;the gold standard, but rarely performed. Indicated if laboratory evidence of iron deficiency anemia is present and no source of blood loss is found.

❖ Treatment:

1. **Oral iron replacement** (FSG) tablets
   - Ferrous Fumarate: 325mg tablet contains 106mg elemental iron
   - Ferrous Sulfate: 325mg tablet contains 65mg elemental iron
   - Ferrous Gluconate: 325mg tablet contains 36mg elemental iron
   - More elemental = more effective = more GI side effects.(gastric upset, constipation)
2. **Parenteral** (IV) **iron replacement.**
   - If not tolerant to oral iron (e.g. significant GI side effects) Or,
   - If blood loss exceeds the capacity of oral iron to meet the needs.
3. **Blood transfusion** is not recommended unless anemia is severe or the patient has cardiopulmonary disease.

Thalassemias:

NO details in the slides

General characteristics:

- Inherited disorders characterized by inadequate production of either the α- or β- globin chain of hemoglobin.
- Low hemoglobin → increase production in the bone marrow → thus we give them transfusion monthly to slow bone marrow production
- They are classified according to the chain that is deficient

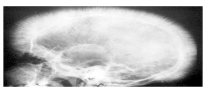
There's 4 alpha and 2 beta. if we missed 2 alpha or one beta its mild. if 3 alpha (HbH) or two beta its severe disease. if 4 alpha missed = hydrops fetalis

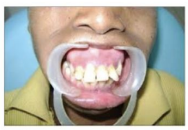
β-Thalassemias: β- chain production is deficient, but the synthesis of α- chains is unaffected.

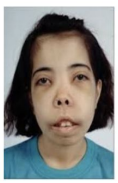
1-Thalassemia major (Cooley anemia; homozygous β-chain thalassemia)—occurs predominantly in Mediterranean populations

a. Clinical features:

- Expansion of bone marrow space "hyperplasia" can cause distortion of bones.
=> Skull x-ray may show "crew-cut" appearance.
- Prominent malar eminences and malalignment of the teeth, secondary to bone marrow hyperplasia.







- Severe anemia (microcytic hypochromic)
- Massive hepatosplenomegaly
- Growth retardation and failure to thrive

b. Diagnosis

- Hemoglobin electrophoresis—Hb F and Hb A2 are elevated. (because they are not formed by beta chains).
- Peripheral blood smear—microcytic hypochromic anemia and target cells may be seen

c. Treatment : frequent PRBC transfusions are required to sustain life (every month), for patients who are 16 years and younger the only cure is bone marrow transplant

2-Thalassemia minor (heterozygous β-chain thalassemia)

- Clinical features: patients are usually asymptomatic. A mild microcytic, hypochromic anemia is the only symptom
- Diagnosis: hemoglobin electrophoresis
- Treatment: usually not necessary (Patients are not transfusion dependent.)

3-Thalassemia intermedia

- Usually involves both β-globin genes
- Severity of anemia is intermediate
- Patients usually are not transfusion dependent

NO details in the slides

α-Thalassemias:

1. **Silent carriers**—mutation/deletion of only one *α*- locus
   a. Asymptomatic
   b. Normal hemoglobin and hematocrit level
   c. No treatment required
2. ***α*-Thalassemia trait (or minor)**—mutation/deletion of two *α*- loci
   a. Characterized by mild microcytic hypochromic anemia
   b. Common in African-American patients
   c. No treatment necessary
3. **Hb H disease**:
   a. Mutation/deletion of **three** *α*-loci.
   b. Severe anemia, the only one that requires treatment.
4. **Mutation/deletion of all four *α*-loci**—results in stillbirths (hydrops fetalis), its called Hb Barts (4 gamma chains).

Iron overload sometimes develops in patients with transfusion-dependent thalassemia, and if untreated this can lead to CHF (symptoms of hemochromatosis). Therefore, these patients are often treated with desferrioxamine (a chelating agent that eliminates excess iron).

Iron deficiency anemia VS Thalassemia

- **Both will have low Hb and low MCV. How to differentiate?**

  In Thalassemia, MCV is disproportionately low to the level of Hb.

- **If iron deficiency anemia is suspected, but the anemia does not respond to iron therapy, obtain a hemoglobin electrophoresis to rule out *α*- and *β*- thalassemia.**

	Iron deficiency anemia	Thalassemia
MCV	Low (80-70s)	Very low (70-60s)
RBC	Low	High or normal
RDW	High	normal
Ferritin/iron level	Low	High or normal

Low Hgb in both but higher in thalassemia 10-11 while in iron deficiency anemia its 9

Normocytic Anemia

Hemolytic Anemia:

Video

- Hemolysis refers to the premature destruction of RBCs due to a variety of causes.
- **Acute drop in Hb is either hemolysis or acute bleeding, so we do hemolytic workup:**

	Hemolysis	Bleeding
MCV	Normal or high	Normal or high
Retics	High	Normal or high
Bleeding	No	Yes, not always apparent
LDH	High	Normal
Haptoglobin	Low	Normal
Indirect bilirubin	High	Normal

- **can be classified according to cause, site, chronicity, or mechanism of destruction:**

- Intracorpuscular defects -Extracorpuscular defects	-Hereditary -Acquired	Site:-Intravascular hemolysis: within the circulation. -Extravascular hemolysis : within the reticuloendothelial system

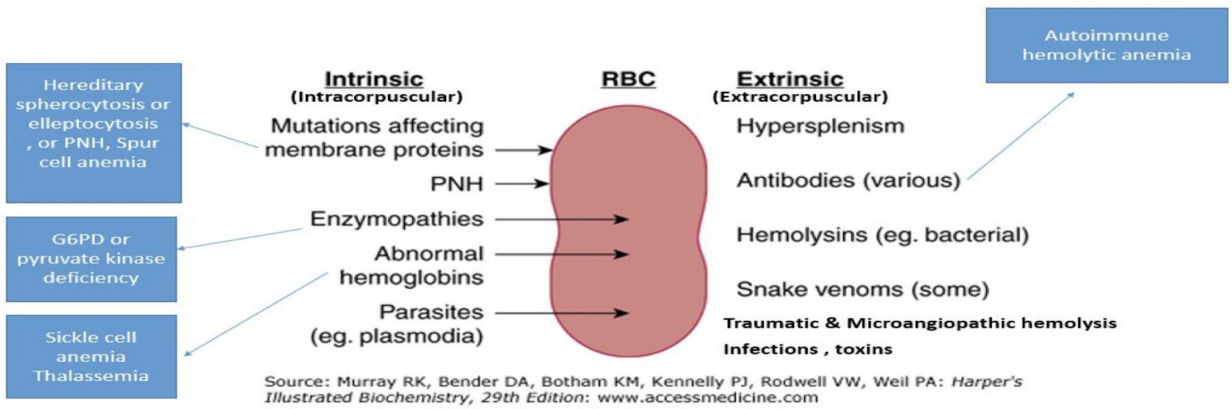
Hemolytic anemias are classified based on cause as follows:

a. Hemolysis due to abnormality extrinsic to RBC—most cases are acquired:

- Immune hemolysis
- Mechanical hemolysis (e.g., prosthetic heart valves, microangiopathic hemolytic anemia)
- Medications, burns, toxins (e.g., snake bite, brown recluse spider bite), infections (e.g., malaria, clostridium)

b. Hemolysis due to intrinsic RBC defects—most cases are inherited:

- Hemoglobin abnormality (e.g., sickle cell anemia, hemoglobin C disease, thalassemias)
- Membrane defects (e.g., hereditary spherocytosis, paroxysmal nocturnal hemoglobinuria [PNH])
- Enzyme defects (e.g., glucose-6-phosphate dehydrogenase [G6PD] deficiency, pyruvate kinase deficiency)



❖ Clinical features:

HEMOLYTIC FACIES- CHIPMUNK FACIES

1. Signs/symptoms of anemia.
2. Jaundice
3. Dark urine color if intravascular process—due to hemoglobinuria, not bilirubin
4. Hepatosplenomegaly, cholelithiasis, and lymphadenopathy if chronic
5. Signs/symptoms of underlying disease (e.g., bone crises in sickle cell disease)

❖ Diagnosis:

1. **Low Hb/Hct**
2. **Elevated reticulocyte count**—due to increased RBC production
3. **Peripheral blood smear**
    a. Schistocytes suggest intravascular hemolysis
    b. Spherocytes or helmet cells suggest extravascular hemolysis (depending on the cause)
    c. Sickled RBCs if sickle cell anemia
    d. Heinz bodies if G6PD deficiency
4. **Low haptoglobin** (especially with intravascular hemolysis)—haptoglobin binds to free Hb, so decreased levels suggest hemoglobin release secondary to RBC destruction
5. **Elevated LDH**—released when RBCs are destroyed
6. **Elevated indirect (unconjugated) bilirubin**—due to degradation of heme as RBCs are destroyed

❖ Treatment:

1. Treat underlying cause
2. Transfusion of PRBCs if severe anemia is present or patient is hemodynamically compromised
3. Folate supplementation—folate is depleted in hemolysis

Treatment of acute bleeding: Hgb less than 7 → transfusion

Anemia of chronic diseases:

-Occurs in the setting of chronic infection (e.g., tuberculosis, lung abscess), malignancy (e.g., lung, breast, Hodgkin disease), inflammation (e.g., rheumatoid arthritis, systemic lupus erythematosus [SLE]), or trauma.

-Which leads to release of inflammatory cytokines(Hepcidin) which has an inhibitory effect on erythropoiesis.

-Generally mild and well tolerated, may be difficult to differentiate from iron deficiency anemia.
-Laboratory findings include:

- Low serum iron
- Normal-to-low TIBC/serum transferrin
- Increased serum ferritin

-Peripheral blood smear usually reveals normocytic and normochromic anemia, but may be microcytic and hypochromic as well.

-No specific treatment is necessary other than treatment of the underlying process—Do not give iron.

Macrocytic Anemia

❖ Megaloblastic:

● Impaired nucleic acid (DNA) metabolism

A. B12 deficiency
B. Folate deficiency
C. C. Drugs(methotrexate):because it interferes with DNA Metabolism.

Vitamin B12 Deficiency:

Video

a. General characteristics:

1. Vitamin B12 is involved in two important reactions.
   - As a cofactor in conversion of homocysteine to methionine.
   - As a cofactor in conversion of methylmalonyl CoA to succinyl CoA.
2. Vitamin B12 stores in the liver are plentiful, and can sustain an individual for 3 or more years.
3. The main dietary sources of vitamin B12 are meat and fish.
4. Vitamin B12 is bound to intrinsic factor (produced by gastric parietal cells), so it can be absorbed by the terminal ileum.

b. Causes:

- Almost all cases are due to impaired absorption.
- Pernicious anemia (lack of intrinsic factor)
- Gastrectomy
- Poor diet (e.g., strict vegetarianism); alcoholism
- Crohn disease, ileal resection (terminal ileum—approximately the last 100 cm)
- Other organisms competing for vitamin B12
  - *Diphyllobothrium latum* infestation (fish tapeworm)
  - Blind loop syndrome (bacterial overgrowth)

C. Clinical features:

- Anemia
- Sore tongue (stomatitis and glossitis)
- **Neuropathy and subacute combined degeneration of the spinal cord——can distinguish between vitamin B12 deficiency and folate deficiency.**
- Demyelination in posterior columns, in lateral corticospinal tracts and spinocerebellar tracts—leads to a loss of position/vibratory sensation in lower extremities, ataxia, and upper motor neuron signs (increased deep tendon reflexes, spasticity, weakness, Babinski sign)
- Can lead to urinary and fecal incontinence, impotence
- Can lead to **dementia**

D. Diagnosis:

1. **CBC:** Hb -->low, MCV high(>100)
2. **Peripheral blood smear.**
   a. Megaloblastic anemia - macrocytic RBCs (MCV >100).
   b. Hypersegmented neutrophils.
3. **Serum vitamin B12 level is low.**
4. **Serum methylmalonic acid and homocysteine levels—**these are **elevated** in vitamin B12 deficiency and are useful if the vitamin B12 level is borderline.
5. **Antibodies against intrinsic factor can help in the diagnosis of pernicious anemia.**
6. **Schilling test—**historically used to determine if B12 deficiency is due to pernicious anemia. Not routinely used now.

E. Treatment: Parenteral therapy is preferred—cyanocobalamin (vitamin B12) IM once per month.

Folate deficiency:

Video

A.General characteristics:

1. Folic acid stores are limited. Inadequate intake of folate over a 3-month period can lead to deficiency.
2. Green vegetables are the main source of folate. Overcooking of vegetables can remove folate**.**

B. Causes :

1. Inadequate dietary intake such as "tea and toast" (most common cause)
2. Alcoholism
3. Long-term use of oral antibiotics
4. Increased demand
5. Pregnancy 'folic acid is essential for all pregnant women'
6. Hemolysis
7. Use of folate antagonists such as **methotrexate**
8. Anticonvulsant medications (phenytoin)
9. Hemodialysis

C. Clinical features: Similar to those in vitamin B12 deficiency **without the neurologic symptoms.**

D. Diagnosis:

1. Peripheral blood smear—reveals megaloblastic (macrocytic) anemia with hypersegmented neutrophils

2. Low serum folate level

3. Elevated serum homocysteine level—methylmalonic acid levels are normal

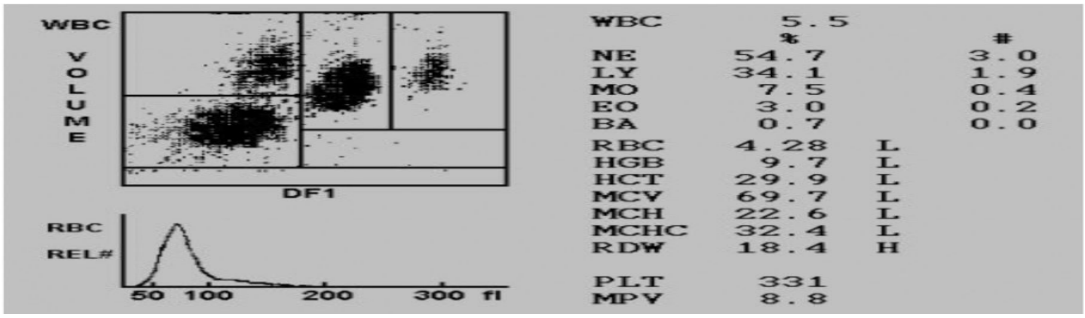
E. Treatment: Daily oral folic acid replacement

❖ Non-Megaloblastic:

- Liver disease, alcohol
- **Myelodysplasia** (MDS)
- Thyroid disease (hypothyroidism)
- Myeloma
- Congenital bone marrow failure syndromes

Cases:

Case 1:

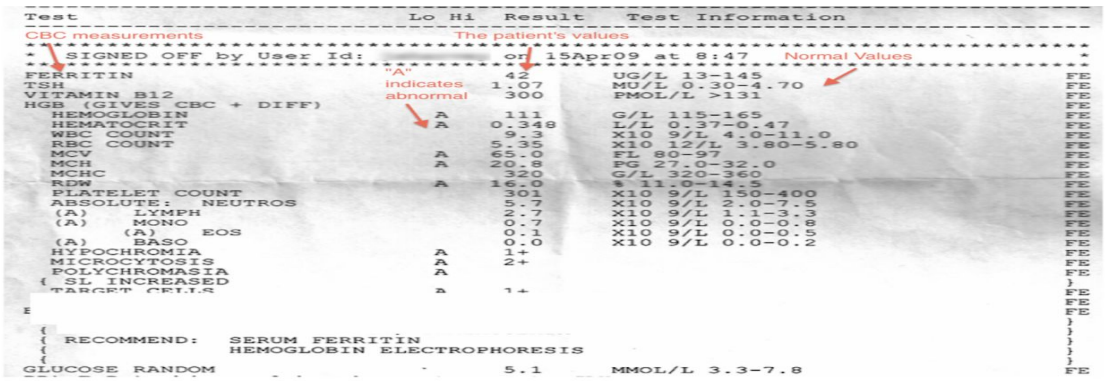


Findings:

1- Hb : low. **2-MCV:**low. **3- RBC count:** low. **4-RDW: high.**

- **Dx:** Most likely IDA

Case 2:

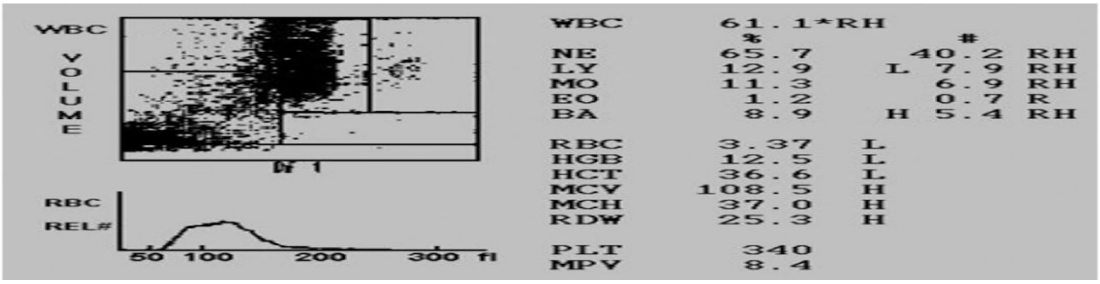


Findings:

1. VERY Low MCV (disproportionate)
2. RBC count is high normal, RDW IS little high
3. Ferritin is **normal**

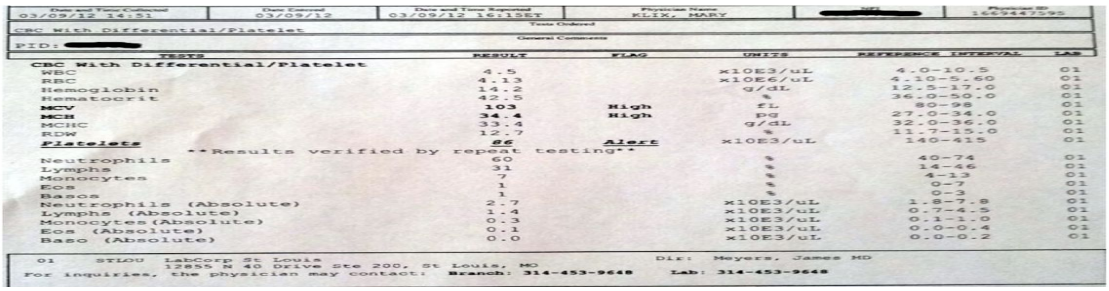
   Dx: Thalassemia

Case 3:



Findings: Macrocytosis, high RDW (Vitamin B12 or folate deficiency)

Case 4:



Findings:1- Macrocytosis 2- Low platelets

Bone Marrow disorder (Myelodysplastic syndrome)

Case 5:

Patient with this CBC findings:

- Hb 5, MCV 85 (normal)?
- What's next? **look for reticulocytes count**
- Retic count was 300 (3%)**

DDx:

1. **Bleeding**
2. **Hemolysis**
3. **Treated nutritional deficiency**

** High reticulocytes count indicates Healthy Bone Marrow =appropriate response

Summary

Anemia definition:

Anemia is defined as a reduction of red cell mass, measured by Hct or Hb concentration. WHO criteria defines anemia as hemoglobin level lower than 12 g/dL in women and 13 g/dL in men.

Approach to anemia

look at 3 CBC parameters + (peripheral blood smear)
1-The hemoglobin (Hb)
2- MCV (micro or normo or macro)
3- Reticulocyte count

Microcytic Anemia

Causes	Clinical feature	Diagnosis	Treatment
1. Iron deficiency anemia (most common type) due: ● Blood loss ● malabsorption ● dietary deficiency (rare) **2. Thalassemia** α-Thalassemia's β-Thalassemia's	**IDA:** ●Glossitis & Angular stomatitis ● Pica (pagophagia) ● koilonychia. ● Pallor. ● Fatigue. ● dyspnea on exertion. ● Tachycardia **Thalassemia's:** **β Major**: Prominent malar eminences and malalignment of the teeth, "crew-cut" appearance, hepatosplenomegaly, microcytic hypochromic, growth retardation. **β Minor**: usually asymptomatic or mild anemia **α-Thalassemias:** -Silent carrier: (asymptomatic) -Trait: Mild anemia -HB H: server anemia -Deletion of all 4 **α**: Hydrops fetalis	**IDA:** **1-Iron studies** a-Decreased serum ferritin (most specific) **2-Peripheral blood smear** **3-Bone marrow biopsy (the gold standard)** **Thalassemia's:** **1-Hemoglobin electrophoresis** (Hb F and Hb A2 are elevated) **2- Peripheral blood smear (target cells)**	**IDA:** 1-Oral iron replacement · 2-Parenteral iron replacement. · 3-Blood transfusion **Thalassemia's** **β Major** frequent PRBC transfusions **β Minor and intermedia** no need. **α-Thalassemia** they don't need any treatment except Hb H

	Iron deficiency anemia	Thalassemia
MCV	Low (80-70s)	Very low (70-60s)
RBC	Low	High or normal
RDW	High	normal
Ferritin/iron level	Low	High or normal

Normocytic Anemia

Causes	Clinical feature	Diagnosis	Treatment
1. Hemolytic Anemia: can be (hereditary or acquired) or (intra/extra vascular) **2. Anemia of chronic disease (inflammatory)**	**1. Hemolytic Anemia**: 1. Signs/symptoms of anemia. 2. Jaundice 3. Dark urine color 4. Hepatosplenomegaly **2. Anemia of chronic disease:** Signs and symptoms of under lying pathology	**1-Hemolytic Anemia** Peripheral blood smear 1-Schistocytes (intra) 2-Spherocytes (extra) 3- Sickled RBCs (SCA) 4-Heinz bodies (G6PD) ↓Hb or Hct ↑Unconjugated bilirubin ↑LDH ↑Reticulocytes ↓Haptoglobin **2. Anemia of chronic disease:** 1-Low serum iron 2-Normal-to-low TIBC/serum transferrin 3-Increased serum ferritin it can be Normochromic or Micro	**1-Hemolytic Anemia:** **1.** Treat underlying cause **2.** Transfusion of PRBCs if severe anemia **3.** Folate supplementation **2. Anemia of chronic disease:** treatment of the underlying process (Do not give iron)

Macrocytic Anemia

Causes	Clinical feature	Diagnosis	Treatment
1) Megaloblastic: 1- B12 deficiency 2- Folate deficiency Drugs (methotrexate) **2) Non-megaloblastic:** 1-liver disease, Alcohol 2-Myelodysplasia 3-thyroid disease (hypothyroidism) 4-Myeloma 5-Congenital bone marrow failure syndrome	**1) Megaloblastic:** Anemia Sore tongue (stomatitis and glossitis) Neuropathy loss of position/vibratory sensation in lower extremities, ataxia, and upper motor neuron signs **Folate have same symptoms but without neuropathy** **2) Non-megaloblastic:** (Underlying pathology)	**1) Megaloblastic:** **1-CBC:** Hb -->low, MCV high(>100) **2-Peripheral blood smear:** a-Megaloblastic anemia b-hypersegmented neutrophils **3-↓serum folate or ↓B12** **4-Serum methylmalonic acid and homocysteine levels** **5-Antibodies against intrinsic factor** **6-Schilling test(B12)**	**B12 deficiency** Parenteral therapy is preferred (cyanocobalamin) IM once/month **Folate deficiency** Daily oral folic acid replacement

Questions

1-) 73-year-old man comes to the office with fatigue that has become progressively worse over the last several months. He is also short of breath when he walks up one flight of stairs. He drinks 4 vodka martinis a day. He complains of numbness and tingling in his feet. On physical examination he has decreased sensation of his feet. His hematocrit is 28% and his MCV is 114 fl (elevated). What is the most appropriate next step in management?

a. Vitamin B12 level
b. Folate level
c. Peripheral blood smear
d. Schilling test

2) A 55-year-old man is being evaluated for constipation. There is no history of prior gastrectomy or of upper GI symptoms. Hemoglobin is 10 g/dL, mean corpuscular volume (MCV) is 72 fL, serum iron is 4 µg/dL (normal 50-150 µg/dL), iron-binding capacity is 450 µg/dL (normal 250-370 µg/dL), saturation is 1% (normal 20%-45%), and ferritin is 10 µg/L (normal 15-400 µg/L). Which of the following is the best next step in the evaluation of this patient's anemia?

a. Red blood cell folate
b. Serum lead level
c. Bone marrow examination
d. Colonoscopy

3)A 50-year-old woman complains of pain and swelling in her proximal interphalangeal joints, both wrists, and both knees. She complains of morning stiffness. She had a hysterectomy 10 years ago. Physical examination shows swelling and thickening of the PIP joints. Hemoglobin is 10.3 g/dL, MCV is 80 fL, serum iron is 28 µg/dL, iron binding capacity is 200 µg/dL (normal 250-370 µg/dL), and saturation is 14%. Which of the following is the most likely explanation for this woman's anemia?

a. Occult blood loss
b. Vitamin deficiency
c. Anemia of chronic disease
d. Sideroblastic anemia

4)A 17-year-old girl complains of fatigue. She has difficulty making it through the entire school day. She recently began to feel her heart beating in her chest. Examination shows pale mucosal membranes. A peripheral blood 'smear shows hypochromic, microcytic red blood cells Which of the following is the most likely diagnosis?

a. Folate Deficiency.
b. Hereditary spherocytosis
c. Iron deficiency anemia
d. Sickle cell anemia

5) A 4 year old girl is brought to her pediatrician for a check up. The child's skin is slightly jaundiced, and she has mild splenomegaly. Her hemoglobin and hematocrit are reduced. Her mean corpuscular volume(MCV) is 90 µm3 and her reticulocyte count is 7%. A Coombs test is performed and is negative. A hemoglobin electrophoresis shows an abnormal component, constituting less than 25% of the total. A blood smear shows inclusion bodies within the RBCs Which of the following is tine most likely diagnosis?

A. Beta thalassemia
B. Heinz body anemia
C. Hereditary spherocytosis
D. Pernicious anemia
E. Sickle cell anemia

6)A 20-year-old black woman' with a history of multiple small bowel resections for Crohn's disease presents complaining of fatigue and dyspnea on exertion. Her physical examination is notable for pallor and a wide-based unsteady gait. Her lab studies reveal a hemoglobin of 10.0 g/dL, witli a mean corpuscular volume(MCV) of 120 µm3. Examination of the peripheral blood smear showed macrocytosis, anisocytosis, poikilocytosis, and neutrophils with 6 to 8 nuclear lobulations. Which one of the following is most likely cause of this patient's anemia?

A. Beta-thalassemia trait
B. Folate deficiency
C. Iron deficiency
D. Sickle cell trait
E. vitamin B12 deficiency

1 (C) | 2 (D) | 3 (C) | 4 (C) | 5 (B) | 6 (E)