Anemia

Objectives:

- Know how to read a CBC (complete blood count)
- Approach to common causes of anemia
- Understand the common terminologies
- Brief overview of investigations and management

Team Members: Khalid Aleisa, Mohammed Bagais,محمد الكحيل, عروب الهذيل

Team Leader: Faris Nafisah

Revised By: abdulaziz aljasser

Resources: 435 team + Davidson + kumar + Recall questions step up to medicine.

- Editing file
- Feedback

Introduction:

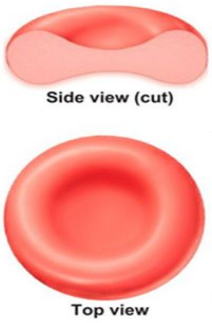
RBCs characteristics:

- Central pallor 1/3rd of RBC volume

What keeps RBC biconcave?

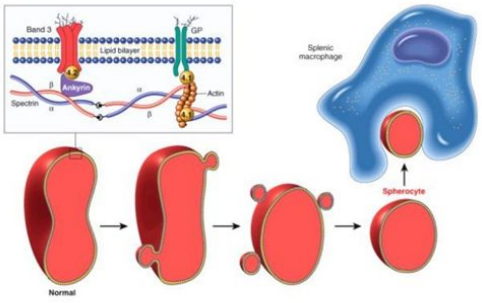
- The cytoskeleton, proteins that keeps the RBC in normal shape.
- Abnormality in one of them → abnormal shape.

- Main function is to carry oxygen
- Biconcave disks
- Essentially bags of hemoglobin; few organelles
- Anucleate (no nucleus)
- Outnumber white blood cells 1000:1
- Contain the plasma membrane protein spectrin and other proteins
- Major factor contributing to blood viscosity

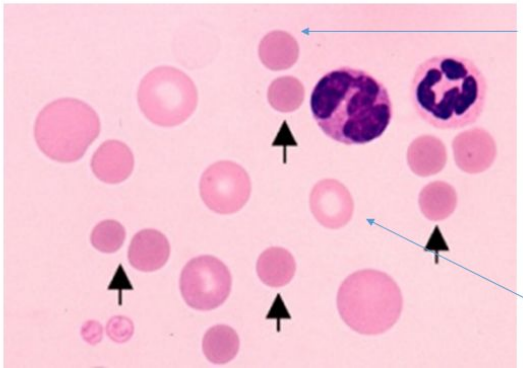


Terminology:

Spherocytosis: (sphere-shaped RBC): sloss of Cytoskeletal proteins => Blebs on the surface => Destroyed by splenic macrophages (extravascular hemolysis). on peripheral smear (loss of central pallor).



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

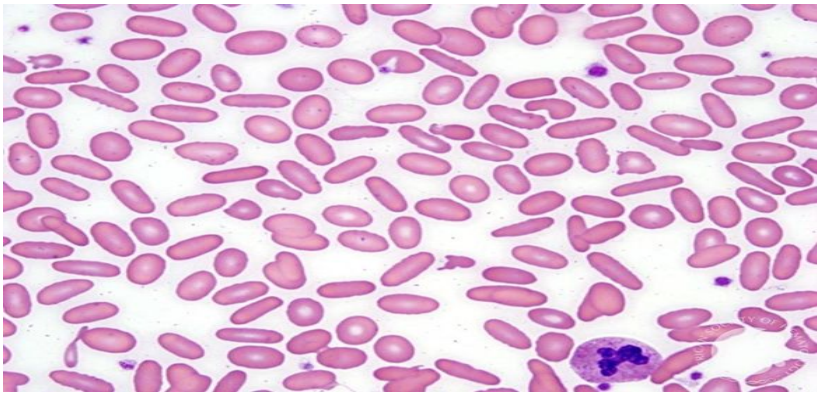


Loss of central pallor "Spherocyte"

Central pallor 1/3rd

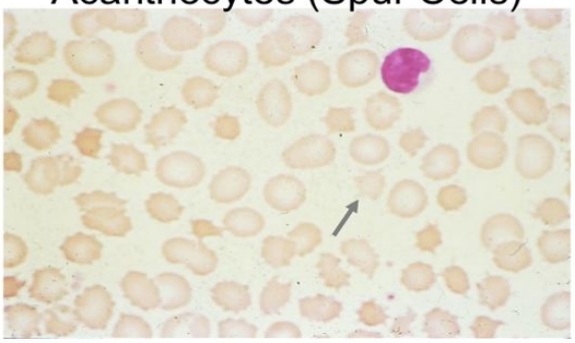
mainly in hemolytic anemia

Elliptocytosis: also known as ovalocytosis



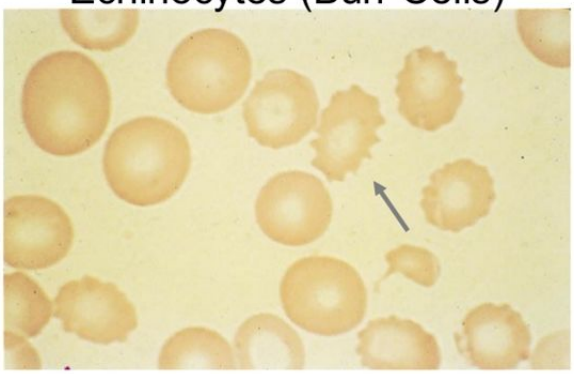
Spur and Burr cells: Both have spikes.

Acanthocytes (Spur Cells)



in Liver disease
very sharp spikes but not symmetrically distributed

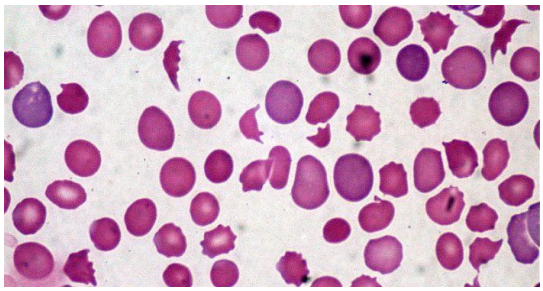
Echinocytes (Burr Cells)



in Renal disease
not very sharp spikes but symmetrical distribution

Schistocytes (Helmet cells):(IMPORTANT)

- Fragmented RBCs, demarcated by two sharp Ends.
- Most important cause is microangiopathic hemolytic anemia (MAHA) caused by thrombotic thrombocytopenic purpura (TTP) => MEDICAL EMERGENCY.
- Also can be caused by DIC



TTP:

is a blood disorder that results in blood clots forming in small blood vessels throughout the body.This results in a low platelet count, low red blood cells due to their breakdown, and often kidneys, heart, and brain dysfunction. Symptoms may include large bruises, fever, weakness

- A fatal disorder with mortality >90% if left untreated.
- Triad: Low platelet count, anemia, schistocytes.
- Pentad: above 3 + (+/- neurological[1] signs or symptoms, +/- renal failure, +/- fever)
- Treatment is **urgent PLasma EXchange** (PLEX) and survival >85% if treated. So, Its highly fatal but highly treatable at the same time.
- TTP is a true medical emergency!
- WHY TTP happen???

  there is protein called (ADAMT13) deficiency of it lead to TTP .

  for more information click here

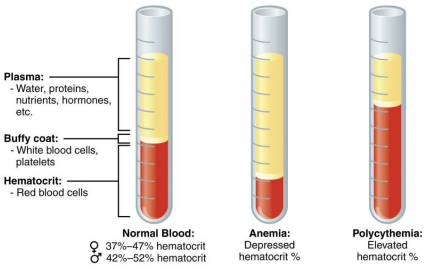
[1] Seizures, stroke, confusion, and Loss of consciousness

Mean corpuscular volume, or mean cell volume (MCV):

- Is a measure of the average volume (=Size) of a red blood corpuscle (or RBC). macro/micro/normocytic
- MCV is calculated from the distribution of individual RBC volumes.

Hematocrit:

- Automated hematocrit (%) is calculated by multiplying the MCV by the RBC number
- Hematocrit = MCV × red blood cells × 100.
- It's the percentage of PRBC to the total volume of blood sample.



Mean corpuscular hemoglobin (MCH):

- Is expressed in picograms.
- The MCH is calculated by dividing hemoglobin (g/L) by red blood cell count (10^12/L).
- It's the average amount or mass OF Hb in ONE CELL.

MCH concentration (MCHC): I look at it only when I suspect spherocytosis

- 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. (If Hb is 15.4 g/dL, hematocrit is 44.1%, MCHC = 15.4/0.441= 34.9g/dL).

RBC distribution width (RDW):

- RDW is the coefficient of variation (differences) of RBCs sizes (called anisocytosis).
- RDW is used in the evaluation of anemia.
- 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.**(IMPORTANT)**
- Myelodysplastic syndromes(lead to bone marrow failure), or RBC transfusions to pts with low/high MCV can produce a dimorphic RBC pattern[2] with a very wide RDW (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).

CBC:

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

[2] Dimorphic is a term used to describe two circulating red cell populations. One is the patient's basic red cell population(normal RBCs); the other is a second population with distinct morphological features.

CBC with differential:

It's very important to order the differential count. Absolute number of differential is more useful than Percentage.

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? 'will be discussed in other lectures'

Neutrophilia:

- **Acute**: bacterial infection, steroids(indigenous , exogenous)[3]
- **Chronic**: Chronic myeloid leukemia (CML)

Lymphocytosis:

- **Acute**: viral infections
- **Chronic**: chronic lymphocytic leukemia (CLL)

Monocytosis:

- Fungal infection, TB, and malignancy.

Eosinophilia:

- Allergic conditions, parasite, autoimmune diseases and eosinophilic leukemia

Basophilia:

- very rare, CML (But not isolated basophilia)

Leukopenia? Which cell line? What degree?

Neutropenia:

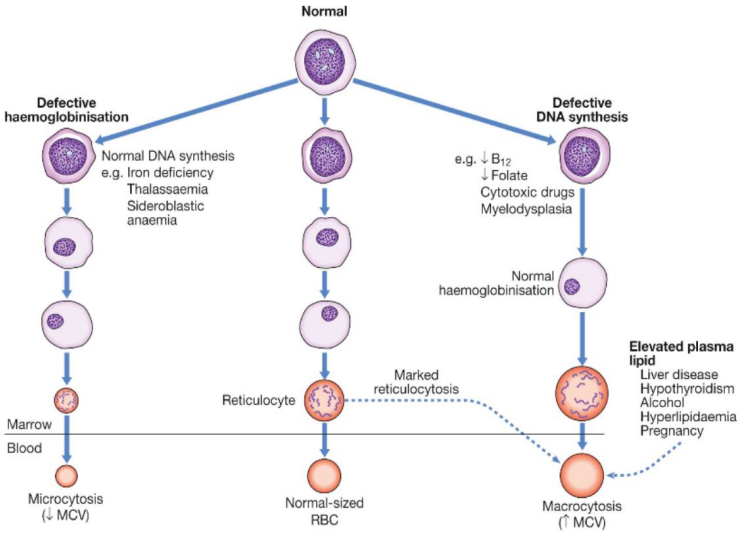
- Mild: Absolute neutrophilic count (ANC) : 1.5 - 1 "X10^9/L", Risk of infection not increased; no need to be investigated (no clinical significance). Mild neutropenia is very common, around 25% of us might have it.
- Moderate: ANC : 1 - 0.5 "X10^9/L", Risk of infection not increased. Needs to be investigated
- Severe: ANC :< 0.5 "X10^9/L", Risk of infection is increased. Must be investigates

CBC Components	Importance
RBC count	Measures the absolute RBC count: 1- Low , 2- Normal, 3- High
Hemoglobin (Hb)	Low: anemia High: polycythemia
Hematocrit (Hct)	Low : anemia High : polycythemia
MCV	Low: Microcytic Normal: Normocytic High: Macrocytic
MCH	Low: Hypochromic Normal: Normochromic
MCHC	High: hereditary spherocytosis
RDW	High: high variation in RBC sizes (anisocytosis) Normal/Low: low or no variation in sizes

[3] Steroids causes demargination of neutrophils from the endovascular wall to the circulation.for more information click here

Introduction to anemia:

- Around 30% of the total world population is anaemic and half of these, about 600 million people, have iron deficiency.
- The principle function of hemoglobin "Hb" is to carry & deliver Oxygen to tissues from the lungs.
- Red cells in the bone marrow must acquire a minimum level of haemoglobin before being released into the bloodstream, If red cells cannot acquire haemoglobin at a normal rate, they will undergo more divisions than normal and will have a low MCV when finally released into the blood.
- A similar defect of cell division is seen where the cell takes hemoglobin normally but undergo fewer cell divisions, resulting in circulating large red cells with a raised MCV.



Definition of anemia:

- anemia is not a diagnosis it's a sign of a disease that's why you always have to ask yourself why the pt is anemic?
- Anemia is defined as a reduction of red cell mass, measured by Hct(sign of acute blood loss) or Hb concentration(10 at least in coronary artery diseases), And O2-carrying capacity
- WHO criteria defines anemia as hemoglobin level lower than 12 g/dL in women and 13 g/dL in men[4]
- 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 (especially if it's gradual), several compensatory mechanisms maintain oxygen delivery to the tissues and delay the appearance of symptoms :**
  - Increased cardiac output (heart rate and stroke volume) → may cause high output heart failure over time (HFpEF).
  - Increased extraction ratio of O2 from Hb[5]
  - Rightward shift of the oxyhemoglobin curve (increased 2,3-diphosphoglycerate [2,3-DPG]) which will result in reduced Hb-O2 affinity.
  - Expansion of plasma volume
  - Tachycardia(because the brain sends message to the heart to pump more oxygenated blood to the brain) and hyperventilation[6]

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

- ◇ The Hb concentration is <7 g/dL
- ◇ The patient requires increased oxygen-carrying capacity (cardiopulmonary disease).
  - ◇ <10 g/dL if he has comorbidities like HF!

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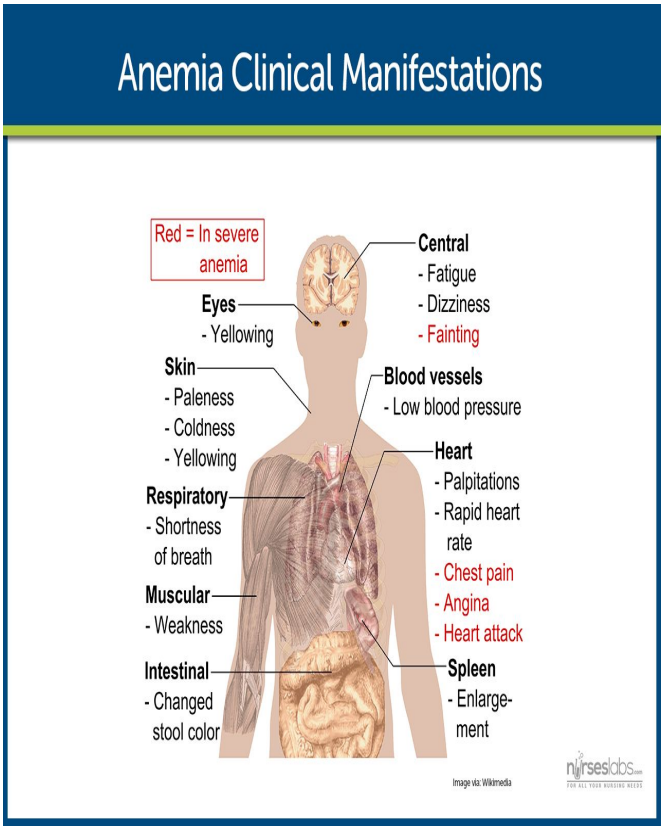
[4] compared to values obtained from a reference population. (2 Standard deviations below normal)

[5] oxygen extraction ratio increases in multiple tissue beds, leading to an increase in the total body oxygen extraction ratio and to a decrease in mixed venous oxygen saturation

[6] So, if anemia develops rapidly, symptoms are more likely to be present, because there is little time for compensatory mechanisms. (symptoms depend on how rapidly the Hb and Hct decrease)

Clinical features of anemia:



- The symptoms and findings of anemia concern many different systems/organs due to the widespread nature of **hypoxia**.
- Anemia is rarely a disease by itself. It is mostly a manifestation or consequence of an underlying (genetic or acquired) disease.
- **Nonspecific complaints and reflect tissue hypoxia:**
  - Headache, fatigue, confusion, decreased mental acuity
  - Diarrhea, nausea, vague abdominal discomfort
  - Dyspnea on exertion
  - Palpitations and Pale skin, hair loss
- **Fatigue, weakness:** active people will complaint from fatigue earlier than less active people
  - Tiredness, lassitude, reduced exercise tolerance
  - Generalized muscular weakness
- **Pallor /skin or mucous membranes:**
  - Pallor best noted in the conjunctiva
  - Skin color may change due to other reasons. eg: Blood flow of skin, subcutaneous fluid , pigment change.
- **Other skin/mucosal changes:**
  - Premature graying of hair:pern anemia
  - Hair loss and fragility + spooning of the nails: iron deficiency anemia
  - Chronic leg ulcers: Sickle cell or other hemolytic anemia
  - Glossitis/burning sense: iron deficiency anemia (rare)
  - Cheilitis (angular stomatitis): iron deficiency anemia
  - Sideropenic dysphagia: iron deficiency anemia
  - Painful ulcerative mouth lesions: aplastic anemia/leukemia
- **Hypotension and tachycardia, palpitation.**
- **Signs of the underlying cause**—jaundice if hemolytic anemia, blood in stool if GI bleeding.

Approach to Anemia:

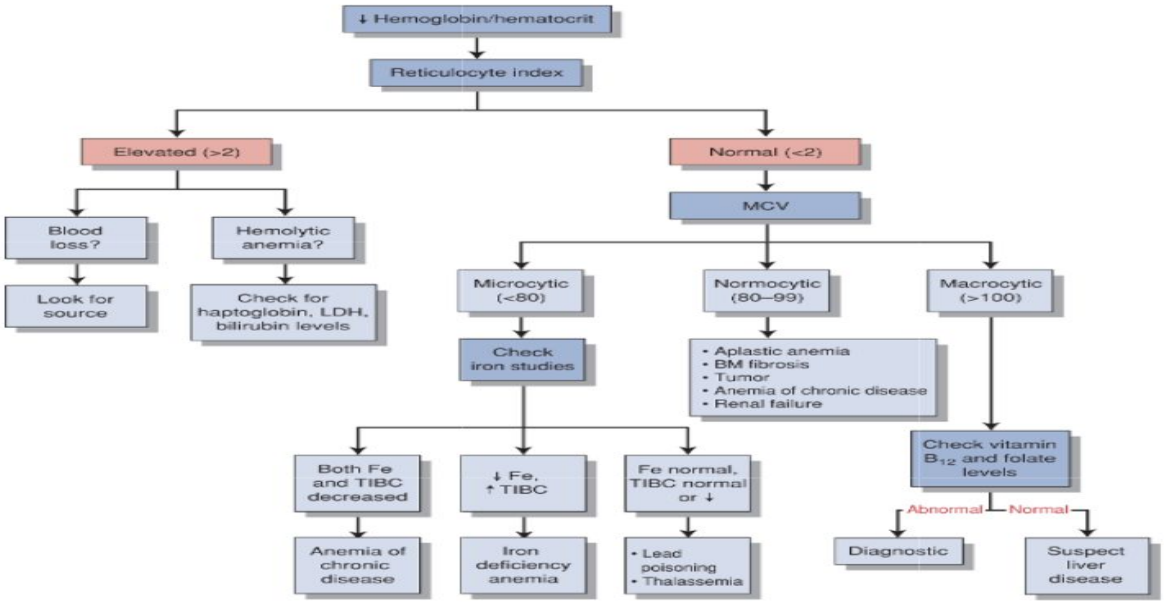
- To start your approach with any case of anemia you need to look at three CBC parameters and one additional test.
- The 3 CBC parameters are:(important) (look at them in the following order)
  - hemoglobin (Hb)
  - MCV to see whether it is microcytic, macrocytic or normocytic
  - Reticulocyte count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

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.
- 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.



Normal Ranges:

- Male: % 0.8 - 2.5
- Female: % 0.8 - 4.1
- corrected Rtc: Patient Hb/Normal Hb x Rtc%
- Reticulocytosis: > 100.000 /mm^3

DDx of anemia: IMPORTANT

MCV < 80 fL (TAILS)	MCV N, low retic count	MCV N, high retic count	MCV > 100 fL
1) Thalassemia 2) Anemia of inflammation 3) Iron deficiency 4) Lead poisoning 5) Sideroblastic anemia **Iron deficiency or thalassemia**	1) **Bone marrow failure:** - Aplastic anemia 2) **BM suppression:** - Toxins, sepsis. - Organ failure: renal failure, liver failure, adrenal insufficiency - Chronic inflammation - chronic diseases 3) **BM infiltration:** - Lymphoma, leukemia - metastatic solid tumour - granulomatous disease (e.g. TB)	**1) Bleeding (acute)** **2) hemolysis** **3) Treated nutritional deficiency** (iron, B12...) These are the only anemic conditions that causes normal MCV with high reticulocytes	1) **Megaloblastic:** (impaired nucleic acid metabolism): - B12 deficiency - folate deficiency - drugs: such as methotrexate (affect DNA synthesis) 2) **Non megaloblastic:** - liver disease - alcohol - Myelodysplasia - thyroid disease - myeloma - Congenital bone marrow failure syndromes

Microcytic Anemia

Iron deficiency anemia: low both MCV and HCV

- Most common cause of anemia worldwide.

Causes:

- **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 (Gastrointestinal blood loss may be exacerbated by the chronic use of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs), inflammatory bowel disease, diverticulitis, polyps and angiodysplastic lesions. hookworm and schistosomiasis are common causes in endemic countries.
- **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 proton pump inhibitors may contribute to the lack of iron availability from the diet.
- **Dietary deficiency/increased iron requirements:**a rare cause

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. **Serum iron (Fe)**: Iron concentration in the blood; **Decreased serum iron in IDA.**
2. **Transferrin**: is the main transport protein for iron: (Increased in IDA)
   i. The body produces transferrin in relationship to the need for iron.
   ii. When iron stores (ferritin) are low, transferrin levels increase and vice versa.
3. **TIBC (Total Iron Binding Capacity)**: (Increased in IDA)
   i. is a measure of all the proteins in the blood that are available to bind with iron (including transferrin).
   ii. The TIBC test is a good indirect measurement of transferrin, as transferrin is the primary iron-binding protein we do both iron and TIBC test To differentiate between IDA and anemia of chronic diseases.
4. **Transferrin saturation (TSAT)**: LOW -> IDA
   i. TSAT is a good marker of iron status.
   ii. TSAT < 20% indicates iron deficiency, a TSAT > 50% may indicate iron overload.
   iii. TSAT: is calculated with:TSAT = (Fe/TIBC) × 100].

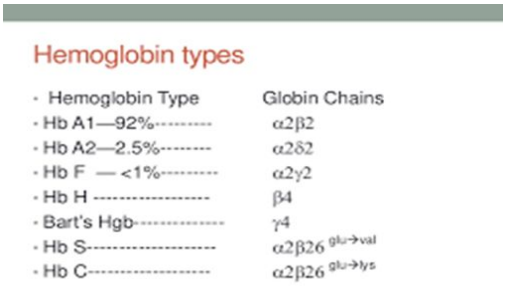
5. **Ferritin level: MOST SPECIFIC ONE (if low → confirm IDA).** if it's high → acute phase reactive. ferritin is the stored iron
6. **Bone marrow biopsy**—the gold standard, but rarely performed. Indicated if laboratory evidence of iron deficiency anemia is present and no source of blood loss is found.

Treatment:

1. **Oral iron replacement (FSG).**
   a. Ferrous Fumarate: 325mg tablet contains 106mg elemental iron
   b. Ferrous Sulfate: 325mg tablet contains 65mg elemental iron
   c. Ferrous Gluconate: 325mg tablet contains 36mg elemental iron
   d. More elemental = more effective = more GI side effects.(gastric upset, constipation)
2. **Parenteral iron replacement.**
   a. If not tolerant to oral iron (e.g. significant GI side effects) Or,
   b. 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:

General characteristics:



- Characterized by "ineffective erythropoiesis[7]" that leads to iron accumulation in the cells (So ferritin is increased).
- Inherited disorders characterized by inadequate production of either the α- or β-globin chain of hemoglobin.
- They are classified according to the chain that is deficient

- ***α*-Thalassemias**
  - There is a decrease in α-chains, which are a component of all types of hemoglobins
  - The β-globin chains bind to each other and form tetramers, which are abnormal hemoglobins and that damage the RBC membrane (This phenomenon occurs mainly with deficiency of three alpha genes a disease known as HbH disease)
  - The severity depends on the number of gene loci that are deleted/mutated—it ranges from an asymptomatic carrier state to prenatal death (hydrops fetalis if 4 alphas are missed)

- ***β*-Thalassemias**
  - β-chain production is deficient, but the synthesis of α-chains is unaffected
  - Excess α-chains bind to each other and form tetramers that damage the RBC membrane
  - It is most often found in people of Mediterranean, Middle Eastern, and Indian ancestry
  - Severity varies with different mutations

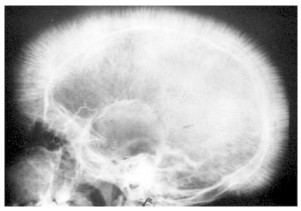
There's 4 alpha and 2 beta. if we missed 2 alpha or one beta its mild.
if 3 alpha (HbH) or two beta its severe disease
if 4 alpha missed = hydrops fetalis

[7] A condition in which there is an active erythropoiesis but with premature death of red blood cells in the bone marrow. Consequently, decreasing RBC output leading to anemia.

β-Thalassemias:

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.
- Severe anemia (microcytic hypochromic)
- Massive hepatosplenomegaly
- Growth retardation and failure to thrive
- If untreated (with blood transfusions), death occurs within the first few years of life secondary to progressive CHF

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.

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

α-Thalassemias:

1.Silent carriers—mutation/deletion of only one *α*-locus

- Asymptomatic
- Normal hemoglobin and hematocrit level
- No treatment required

***2.α*-Thalassemia trait (or minor)**—mutation/deletion of two *α*-loci

- Characterized by mild microcytic hypochromic anemia
- Common in African-American patients
- No treatment necessary

3.Hb H disease:

- Mutation/deletion of **three** *α*-loci.
- 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).

- **How to differentiate between Iron deficiency anemia and Thalassemia by CBC?** 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 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). **(important)**

	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 Normal MCV and MCH

Hemolytic Anemia:

- **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

Hemolytic anemias:

- **Can be classified as:**
  - Hemolysis due to intracorpuscular defects
  - Hemolysis due to extracorpuscular defects

Or

  - Hereditary hemolytic diseases
  - Acquired hemolytic diseases

Or

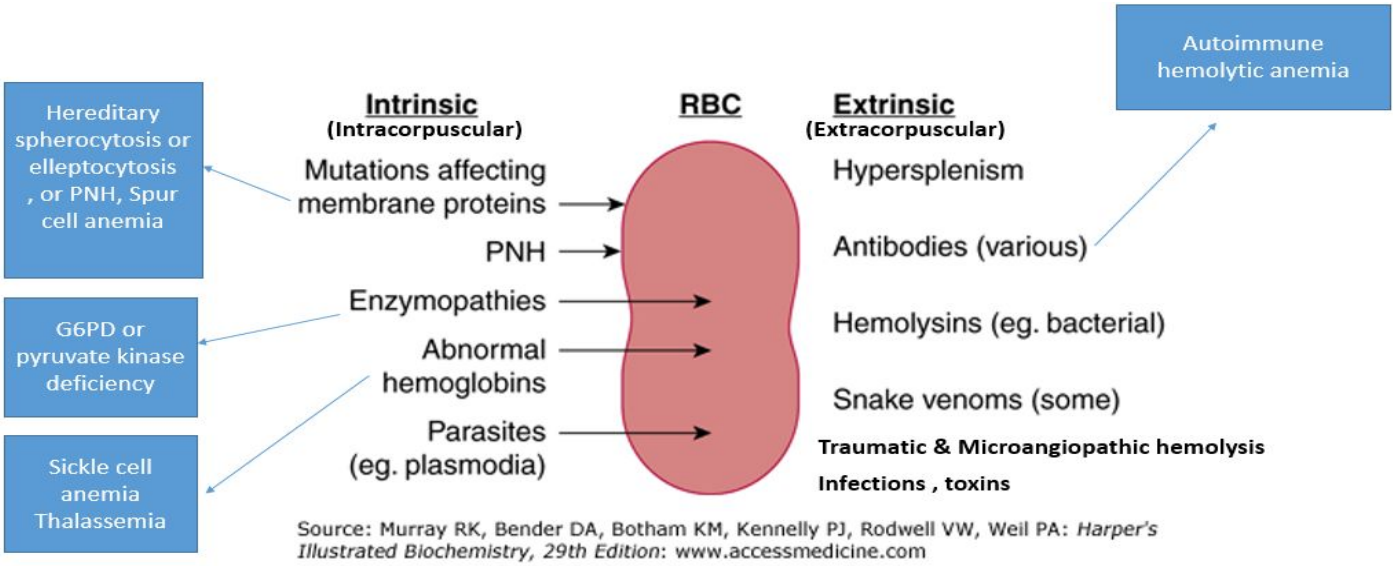
  - intravascular hemolysis: within the circulation.
  - extravascular hemolysis : within the **reticuloendothelial system, primarily the spleen.**
  - In most haemolytic states, haemolysis is predominantly extravascular.

I- Hallmarks of haemolysis: for both extra and intravascular types.

- ↓Haemoglobin or Hct it's ANEMIA!
- ↑Unconjugated bilirubin (due to degradation of heme) Jaundice
- ↑Lactate dehydrogenase (LDH is released when RBCs are destroyed) high LDH is lymphoma until proven otherwise
- ↑Reticulocytes
- ↑Urinary urobilinogen

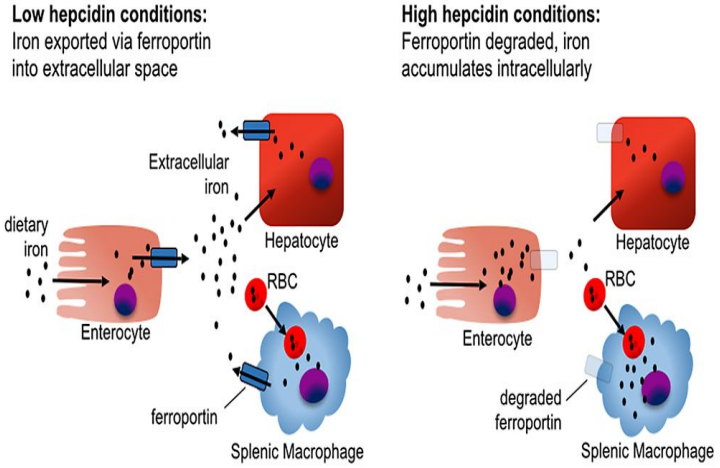
II- Additional features of intravascular haemolysis:

- ↓Haptoglobin (Haptoglobin is released from the liver and binds to hemoglobin, so its absence means that hemoglobin was destroyed and haptoglobin has already been depleted)
- ↑Methemalbumin
- Positive urinary haemosiderin
- **Haemoglobinuria**
- Hemolysis can be due to either intrinsic (**Intracorpuscular)** factors in RBC itself, or extrinsic (**Extracorpuscular)** factors:
  - all intrinsic factors are hereditary **Except** paroxysmal nocturnal hemoglobinuria (PNH) and spur cell anemia, these two are acquired
  - all extrinsic factors are acquired



Anemia of chronic disease:

It can be normocytic or microcytic!



- Ferroportin is an Exporter that excretes iron from the inside of a cell to outside.
- Hepcidin is an acute phase reaction protein that is excreted by liver. It degrades ferroportin, so iron accumulates in the cells (Iron restriction).
- This leads to anemia due to an inadequate amount of serum iron available for erythropoiesis
- Occurs in the setting of chronic infection (e.g., tuberculosis, lung abscess), cancer (e.g., lung, breast, Hodgkin disease), inflammation (rheumatoid arthritis, SLE), or trauma.
- Which leads to release of inflammatory cytokines (Hepcidin) which has an inhibitory effect on erythropoiesis.
- you may see a combination of anemia of chronic diseases and iron deficiency anemia
- Laboratory findings:
    - Serum iron is low.
    - TIBC is low.
    - Transferrin saturation is normal or low normal.
    - Serum ferritin levels are increased.
- The anemia is **mostly normocytic and normochromic, but may be microcytic and hypochromic as well.**
- No specific treatment is necessary other than treatment of the underlying process. The anemia is usually mild and well tolerated.
- **Do not give iron.**

Macrocytic Anemia

Megaloblastic:

- **Impaired nucleic acid (DNA) metabolism**
  A. B12 deficiency
  B. Folate deficiency
  C. Drugs (methotrexate) : because it interferes with DNA Metabolism.

Vitamin B12 Deficiency:

a. General characteristics:

1. Vitamin B_{12} 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 B_{12} stores in the liver are plentiful, and can sustain an individual for 3 or more years.
3. The main dietary sources of vitamin B_{12} are meat and fish.
4. Vitamin B_{12} is bound to intrinsic factor (produced by gastric parietal cells), so it can be absorbed by the terminal ileum.

b. Causes:

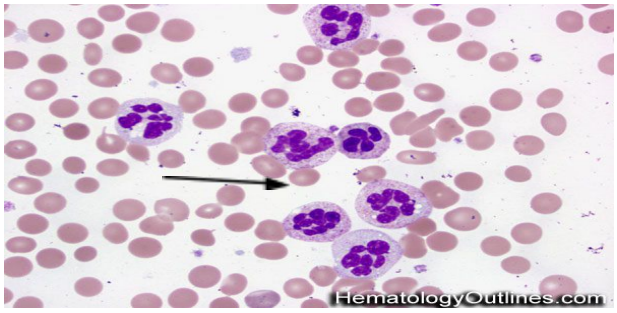
- almost all cases are due to impaired absorption)
- Pernicious anemia (lack of intrinsic factor) - most common cause in the Western hemisphere
- Gastrectomy no IF?
- Poor diet (e.g., strict vegetarianism); alcoholism
- Crohn disease, ileal resection (terminal ileum—approximately the last 100 cm)
- Other organisms competing for vitamin B_{12}
  - *Diphyllobothrium latum* infestation (fish tapeworm)
  - Blind loop syndrome (bacterial overgrowth)

c. Clinical features:

- Anemia
- Sore tongue (stomatitis and glossitis)
- **Neuropathy—can distinguish between vitamin B_{12} deficiency and folate deficiency,** if the vitamin B_{12} deficiency remains untreated, **irreversible** neurologic disease can result.
- 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)[8]
- Can lead to urinary and fecal incontinence, impotence
- Can lead to **dementia**

[8] Subacute combined degeneration of the spinal cord

d. Diagnosis:



1. **CBC:**Hb -->low, MCV high(>100)
2. **Peripheral blood smear.**
   - Megaloblastic anemia - macrocytic RBCs (MCV >100).
   - Hypersegmented neutrophils.
3. **Serum vitamin B_{12} level is low.**
4. **Serum methylmalonic acid and homocysteine levels**—these are **elevated** in vitamin B_{12} deficiency and are useful if the vitamin B_{12} level is borderline.
5. **Antibodies against intrinsic factor can help in the diagnosis of pernicious anemia.**
6. **Schilling test**—historically used to determine if B_{12} deficiency is due to pernicious anemia. Not routinely used now.
   - Give an IM dose of unlabeled vitamin B_{12} to saturate binding sites.
   - Give an oral dose of radioactive vitamin B_{12}; measure the amount of vitamin B_{12} in urine and plasma to determine how much vitamin B_{12} was absorbed.
   - Repeat the test (oral radioactive vitamin B_{12}) with the addition of intrinsic factor. If malabsorption is the problem, adding intrinsic factor will not do anything. However, if pernicious anemia is present, adding intrinsic factor will improve serum vitamin B_{12} levels.

e. Treatment:

- Parenteral therapy is preferred—cyanocobalamin (vitamin B_{12}) IM once per month.

Folate deficiency:

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 B_{12} deficiency **without the neurologic symptoms.**

d. **Treatment**

- **Daily oral folic acid replacement**

Non-Megaloblastic:

you need to know that these conditions can cause megaloblastic anemia

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

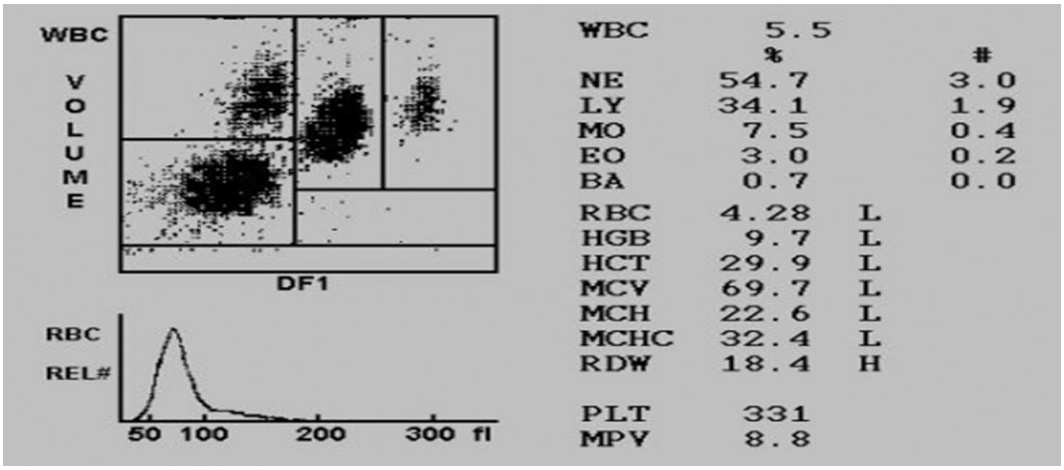
Myelodysplastic syndromes (MDS):

- **A heterogeneous group of malignant hematopoietic stem cell disorders**
- **Characterized by:**
  - Dysplasia (abnormal morphology)
  - Varying degree of cytopenia
  - Variable risk of transformation to AML
  - A disease of the elderly (median age >65)
- **Treatment:**
  - Supportive (transfusion, GCSF[9], antibiotics, EPO)
  - Hypomethylating agents (azacitidine)
  - Stem cell transplant (younger patients without comorbidities)

Cases

Case 1:

- Read this CBC



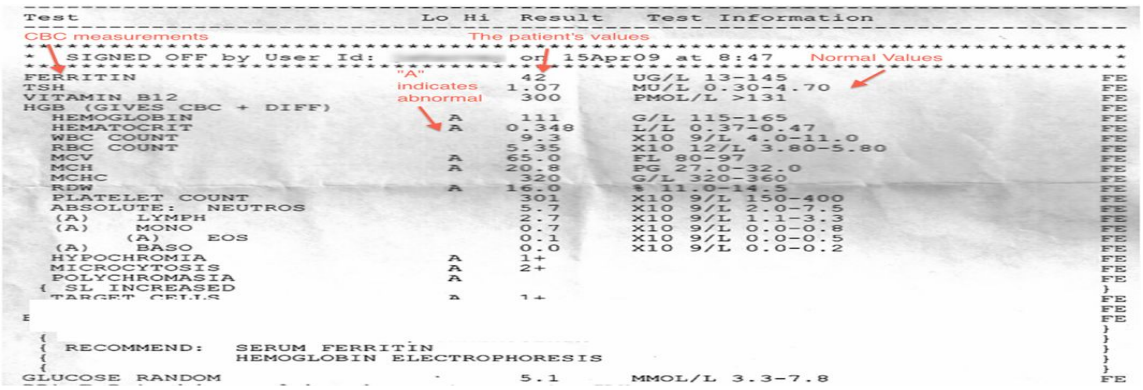
Findings:

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

- **Dx: Most likely IDA**

[9] granulocyte colony stimulating factors

Case 2:



Test	Lo Hi	Result	Test Information
CBC measurements		The patient's values	
SIGNED OFF by User Id: [redacted] on 15Apr09 at 8:47			Normal Values
FERRITIN		42	UG/L 13-145
TSH		1.07	MU/L 0.30-4.70
VITAMIN B12		300	PMOL/L >131
HGB (GIVES CBC + DIFF)			
HEMOGLOBIN	A	111	G/L 115-165
HEMATOCRIT	A	0.348	L/L 0.37-0.47
WBC COUNT		9.3	X10 9/L 4.0-11.0
RBC COUNT		5.35	X10 12/L 3.80-5.80
MCV	A	65.0	FL 80-97
MCH	A	20.8	PG 27.0-32.0
MCHC		320	G/L 320-360
RDW	A	16.0	% 11.0-14.5
PLATELET COUNT		301	X10 9/L 150-400
ABSOLUTE: NEUTROS		5.7	X10 9/L 2.0-7.5
(A) LYMPH		2.7	X10 9/L 1.1-3.3
(A) MONO		0.7	X10 9/L 0.0-0.8
(A) EOS		0.1	X10 9/L 0.0-0.5
(A) BASO		0.0	X10 9/L 0.0-0.2
HYPOCHROMIA	A	1+	
MICROCYTOSIS	A	2+	
POLYCHROMASIA	A		
SL INCREASED			
TARGET CELLS	A	1+	
RECOMMEND: SERUM FERRITIN			
HEMOGLOBIN ELECTROPHORESIS			
GLUCOSE RANDOM		5.1	MMOL/L 3.3-7.8

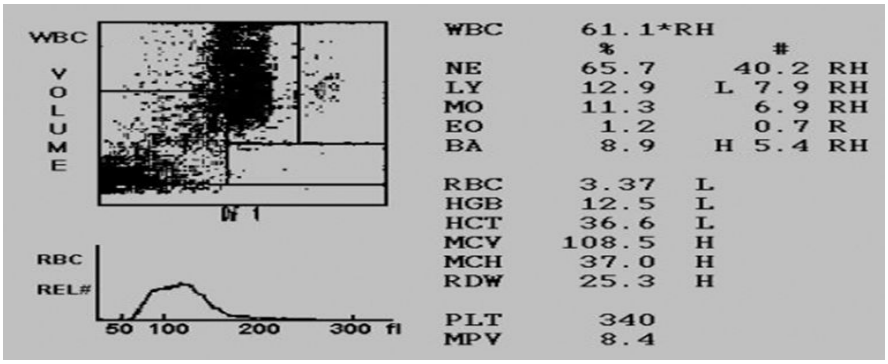
"A" indicates abnormal

Findings:

- VERY Low MCV (disproportionate)
- RBC count is <u>high normal</u>, RDW IS little high
- Ferritin is **<u>normal</u>**

Dx: Thalassemia

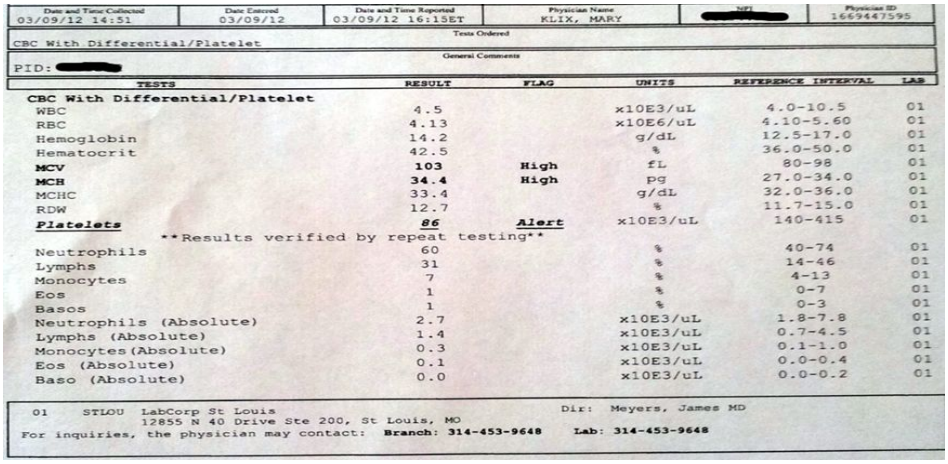
Case 3:



WBC	61.1*RH		
	%		#
NE	65.7		40.2 RH
LY	12.9	L	7.9 RH
MO	11.3		6.9 RH
EO	1.2		0.7 R
BA	8.9	H	5.4 RH
RBC	3.37	L	
HGB	12.5	L	
HCT	36.6	L	
MCV	108.5	H	
MCH	37.0	H	
RDW	25.3	H	
PLT	340		
MPV	8.4		

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

Case 4:



Date and Time Collected	Date Entered	Date and Time Reported	Physician Name	MR#	Physician ID
03/09/12 14:51	03/09/12	03/09/12 16:15ET	KLIX, MARY	[redacted]	16694475795

Tests Ordered: CBC With Differential/Platelet

General Comments: PID: [redacted]

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
CBC With Differential/Platelet					
WBC	4.5		x10E3/uL	4.0-10.5	01
RBC	4.13		x10E6/uL	4.10-5.60	01
Hemoglobin	14.2		g/dL	12.5-17.0	01
Hematocrit	42.5		%	36.0-50.0	01
MCV	**103**	**High**	fL	80-98	01
MCH	**34.4**	**High**	pg	27.0-34.0	01
MCHC	33.4		g/dL	32.0-36.0	01
RDW	12.7		%	11.7-15.0	01
Platelets	***86***	***Alert***	x10E3/uL	140-415	01
Results verified by repeat testing					
Neutrophils	60		%	40-74	01
Lymphs	31		%	14-46	01
Monocytes	7		%	4-13	01
Eos	1		%	0-7	01
Basos	1		%	0-3	01
Neutrophils (Absolute)	2.7		x10E3/uL	1.8-7.8	01
Lymphs (Absolute)	1.4		x10E3/uL	0.7-4.5	01
Monocytes(Absolute)	0.3		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

01 STLOU LabCorp St Louis
12855 N 40 Drive Ste 200, St Louis, MO
Dir: Meyers, James MD
For inquiries, the physician may contact: Branch: 314-453-9648 Lab: 314-453-9648

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

Extra:

Aplastic Anemia: Bone marrow failure leading to pancytopenia (anemia, neutropenia, thrombocytopenia).

diagnosis: Normocytic, normochromic anemia. bone marrow biopsy (definitive diagnosis)

Rx: Bone marrow transplantation

Sickle cell anemia: Autosomal recessive disorder that results when the normal Hb A is replaced by the mutant Hb S. Sickle cell disease is caused by inheritance of two Hb S genes.

*High-output heart failure may occur over time , many adults eventually die of CHF

diagnosis:

1- Anemia is the most common finding.

2- Peripheral smear:sickle-shaped RBCs

3- Hemoglobin electrophoresis : - required for definitive diagnosis. - demonstrate the absence of HbA, 2–20% HbF and the predominance of HbS(~80%)

Rx:

- Folic acid supplements (due to chronic hemolysis).
- Hydroxyurea
- Blood transfusion

G6PD deficiency hemolytic anemia.

Autoimmune hemolytic anemia.

Summary:

Approach to Anemia:

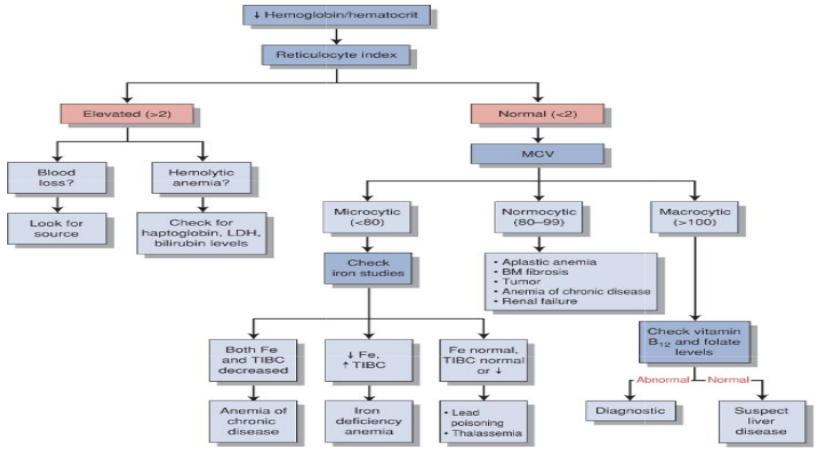
look at 3 CBC parameters + (peripheral blood smear)

1-The hemoglobin (Hb) 2- MCV (micro or normo or macro) 3- Reticulocyte count

Types according to MCV	Microcytic	Normocytic	Macrocytic
Causes	**1.** Iron deficiency anemia (most common type of anemia) due to: ● Blood loss ● malabsorption ● dietary deficiency (rare) **2.** Thalassemia ü α-Thalassemia's ü β-Thalassemia's	**1. Hemolytic Anemia** a. can be (hereditary or acquired) or (intra/extra vascular) **2. Anemia of chronic disease** (inflammatory)	**1) Megaloblastic:** · B12 deficiency · Folate deficiency · Drugs (methotrexate) **2) Non-megaloblastic:** · liver disease, alcohol · Myelodysplasia · thyroid disease (hypothyroidism) · myeloma . Congenital bone marrow failure syndrome
Clinical feature	**IDA:** Glossitis and Angular stomatitis ● **Pica (pagophagia)** ● koilonychia. ● Pallor. ● Fatigue. ● dyspnea on exertion. ● Tachycardia **Thalassemia's:** **β Major:** "crew-cut" appearance, hepatosplenomegaly, growth retardation. **β Minor:** asymptomatic/mild anemia **α** **-Silent carrier:** (asymptomatic) **-Trait:** Mild anemia -HB H: server anemia **-Deletion of 4:** Hydrops fetalis	**1. Signs and symptoms of anemia** **2. Signs and symptoms of under lying pathology (example: rheumatoid arthritis, joint pain)**	**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** **Non-Megaloblastic (Underlying pathology)**

Diagnosis	**-IDA:** · **Bone marrow biopsy**—the gold standard · **Ferritin level (MOST SPECIFIC)** · **Serum iron (Fe)** · **Transferrin** · **TIBC** · **Transferrin saturation** **-Thalassemia's:** · **Hemoglobin electrophoresis** · **Peripheral blood smear (target cells/ Normo Hypo RBC)** · **In IDA MCV is Low, but in Thalassemia MCV is very low**	**Hemolytic** **Both Extra/Intra vascular:** · ↓Hb or Hct · ↑Unconjugated bilirubin · ↑LDH · ↑Reticulocytes · ↑Urinary urobilinogen **Intravascular:** ↓Haptoglobin ↑Methemoglobin Hemoglobinuria **Anemia of chronic Disease** · Serum iron is low. · TIBC is low. · Transferrin saturation is normal or low normal. · Serum ferritin levels are increased. · ***it can be Normochromic or Micro***	**Megaloblastic** 1. **CBC:** Hb -->low, MCV high (>100) **2 .Peripheral blood smear.** • Hyper-segmented neutrophils • Macrocytic R • **Serum vitamin B_{12} level.** • **Serum methylmalonic acid and homocysteine levels**. • **Antibodies against intrinsic factor** • **Schilling test** **NON-Megaloblastic** N/A
Treatment	**IDA** · **Oral iron replacement** · **Parenteral iron replacement.** · **Blood transfusion** **Thalassemia's** **β Major** frequent PRBC transfusions **β Minor and intermedia no need.** **α** they don't need except **Hb H**	-No specific treatment is necessary other than treatment of the underlying process. **-Do not give iron.**	**B12** à Parenteral therapy is preferred— (vitamin B_{12}) IM **Folate** à **Daily oral folic acid replacement** MDS à · Supportive (transfusion, GCSF, antibiotics, EPO) · Hypomethylating agents (azacitidine) · Stem cell transplant (younger patients without comorbidities)

MCV < 80 fL (TAILS)	MCV N, low retic count	MCV N, high retic count	MCV > 100 fL
1) Thalassemia 2) Anemia of inflammation 3) Iron deficiency 4) Lead poisoning 5) Sideroblastic anemia **Iron deficiency or thalassemia**	1) **Bone marrow failure:** - Aplastic anemia 2) **BM suppression:** - Toxins, sepsis. - Organ failure: renal failure, liver failure, adrenal insufficiency - Chronic inflammation - chronic diseases 3) **BM infiltration:** - Lymphoma, leukemia - metastatic solid tumour - granulomatous disease (e.g. TB)	1) **Bleeding (acute)** 2) **hemolysis** 3) **Treated nutritional deficiency** (iron, B12...) These are the only anemic conditions that causes normal MCV with high reticulocytes	1) **Megaloblastic:** (impaired nucleic acid metabolism): - B12 deficiency - folate deficiency - drugs: such as methotrexate (affect DNA synthesis) 2) **Non megaloblastic**: - liver disease - alcohol - Myelodysplasia - thyroid disease - myeloma - Congenital bone marrow failure syndromes



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

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