Lecture 66

Editing file

Medicine Team

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Anemia

Objectives:

- ★ Formulate an approach to reading CBC
- ★ List the causes of microcytic, normocytic and macrocytic anemia
- ★ Differentiate between the different causes of anemia
- ★ Describe the different terms used in hematology
- ★ Discuss brief management plan for common causes of anemia

The main objectives of this lectures is to learn how to read CBC (it's such an essential test that you will have to know how to read and interpret regardless of what speciality you end up doing)

Color index:

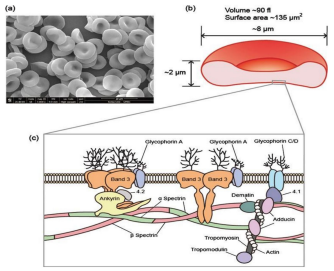
Original text Females slides Males slides
Doctor's notes Textbook Important Golden notes Extra

Introduction

◀ RBC

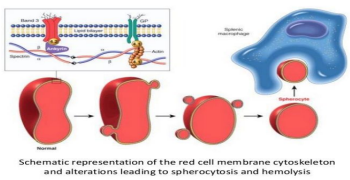
1. Main function is to carry oxygen to the tissue
2. Biconcave disks
3. Essentially bags of hemoglobin (full of Hb); few organelles
4. Anucleated (no nucleus)
5. Outnumbers WBC 1000:1
6. Contains the plasma membrane protein spectrin and other proteins
7. Major factor contributing to blood viscosity

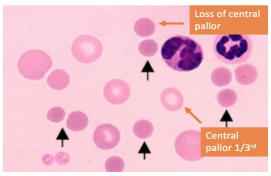
◀ What Keeps RBCs BiConcave?



- Due to the cytoskeleton. Part of it is vertically oriented (like: Band 3 and Ankyrin.. etc), While some are horizontally oriented (like alpha spectrin and beta spectrin etc). These proteins help keeping the RBCs biconcave. Abnormalities of these proteins it could lead to change in the shape of RBC.

◀ Terminology





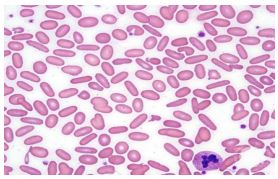
Spherocytosis (sphere-shaped RBC)

- Change of the biconcave shape of RBC to Sphere-like or ball-like shape
- Due to different reasons (typically because of the abnormality present in cell membrane, when RBC circulate into macrophages in spleen, the spleen eats apportion of the RBC → becomes a spherocyte.
- Under the microscope, there is **loss of central pallor** (normally ⅓ of RBC center is pale), loss of central pallor will make the RBC looks red throughout.
- **Hereditary spherocytosis:**
  - Usually inherited as an autosomal dominant condition
  - The most common abnormalities are deficiencies of beta spectrin or ankyrin
  - Most cases are associated with an asymptomatic compensated chronic haemolytic state with spherocytes present on the blood film, a reticulocytosis and mild hyperbilirubinaemia.
  - Occasional cases are associated with more severe haemolysis; these may be due to coincidental polymorphisms in alpha spectrin or co-inheritance of a second defect involving a different protein.
  - **Presentation:**
    - A *haemolytic crisis* occurs when the severity of haemolysis increases; usually associated with **infection.**
    - A megaloblastic crisis follows the development of **folate deficiency**; this may occur as a first presentation of the disease in **pregnancy**.
    - An aplastic crisis occurs in association with **parvovirus** (erythrovirus) infection.
  - **Investigations:**
    - Haemoglobin levels: variable
    - Blood film: spherocytes
    - Direct Coombs test: negative → excludes immune haemolysis.
    - Osmotic fragility test: may show increased sensitivity to lysis in hypotonic saline solutions but is limited by lack of sensitivity and specificity.
    - Flow cytometric tests: More specific → binding of eosin-5-maleimide to red cells.
  - **Management:** Folic acid prophylaxis, 5 mg daily, should be given for life.

Introduction *(cont.)*

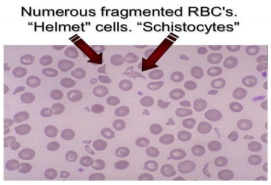
◄ Terminology *(cont.)*

Elliptocytosis (Also known as ovalocytosis)



- Clinically it is a similar condition to HS but milder.
- RBC look like Cylindrical in shape "اسطوانية الشكل", we call them "Elliptocyte".
- Elliptocytosis is when you have lots of elliptocyte
- could be either congenital anemia (inherited) or related to some nutritional deficiencies like iron deficiency.
- **Hereditary elliptocytosis:** a heterogeneous group of disorders that produce an increase in elliptocytic red cells on the blood film and a variable degree of haemolysis
    - Due to abnormality of one or more anchor proteins in the red cell membrane, e.g. alpha spectrin or protein 4.1
    - leads to haemolytic anemia
    - Management: similar to hereditary spherocytosis

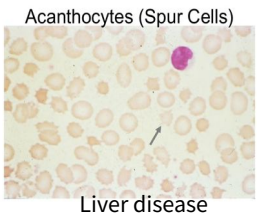
Schistocytes (Helmet Cells)



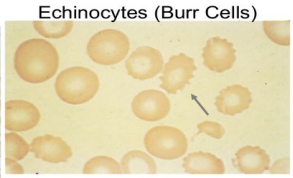
- Under the microscope, RBCs look like a helmet ⛑, they have sharp ends (disrupted RBC). Can be seen in microangiopathic hemolytic anemia (MAHA), in which there's pathologic formation of platelet microthrombi in small vessels leading to shearing of RBCs as they cross the microthrombi (e.g. TTP)
- These cells are very important in condition called **Thrombotic thrombocytopenic purpura "TTP"**[2] which is a **medical emergency** that may lead to thrombosis and possibly death. It's also seen in DIC.
- Thus, finding schistocytes in peripheral blood could indicate a serious disorder.

Spur and Burr Cells

- **Acanthocytes:** different spikes in RBC that are **not evenly distributed**, some of them are quite **sharp**. Happen usually in **liver disease**
- **Echinocytes:** again spikes in RBC as Acanthocytes but they're **not sharp** as acanthocytes, and they are **evenly distributed.** Happen usually in **renal disease**



Liver disease



Renal disease

◄ RBCs indices

1 MCV[1]

The **Mean Corpuscular Volume**, or **Mean Cell Volume**

- 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.
- **Normal range: 77-95 fl**

2 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 RBC count (x10^{12}/L).**
- **Normal range: 27-34 picogram**

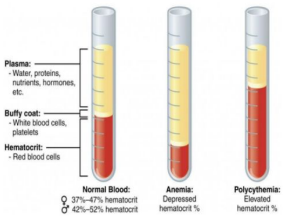
1: Although it says volume there, it only refers to the average ***size*** of the RBC. High: "big RBCs → macrocytic". Low: "small RBCs → microcytic"
2: It's due to ADAMTS13 deficiency, an enzyme that normally cleaves vWF multimers into smaller monomers for eventual degradation. Lab findings: Thrombocytopenia with normal PT/PTT.

Introduction *(cont.)*

◀ RBCs indices *(cont.)*

3 Hematocrit

- Automated hematocrit (%) is calculated by multiplying the MCV by the RBC number.
- Hematocrit = MCV x absolute RBCs count x 100.
- When we take a blood sample, you put it in centrifugation machine, it will separate the blood into the packed RBC volume, puffy coat WBC and plasma
  As seen in the pic



In anemia, packed RBC "hematocrit" will be low. In polycythemia the packed RBC "hematocrit" is increased

4 MCHC
(Mean corpuscular hemoglobin concentration)

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 (%) x 100.[1]
- **Normal range:** 32-36 mg/dL
- **High → hereditary spherocytosis**

5 Red Blood Cell Distribution Width (RDW)

- RDW is a measure of the **degree of anisocytosis (variation in RBC size)**
  - **Normal/Low:** Low or No variation in sizes
  - **High:** High variation in RBC sizes (Anisocytosis)
- It's used in the **evaluation** of anemia → Very important marker
- More frequently elevated with microcytic anemias "Low MCV" due to **iron deficiency anemia** than to thalassemia or anemia of chronic disease.
- More frequently with macrocytic anemias "High MCV" due to **vitamin B12 or folate deficiency** anemia than to liver disease, hypothyroidism.
- **Myelodysplastic syndromes** (usually transfused patient, and even without transfusion because of different development of red blood cells, they have different sizes and → elevated RDW), or RBC transfusions to patients with low/high MCV can produce a dimorphic RBC pattern with a high RDW value.
  Why? Because if you transfused RBCs from a donor, the recipient will have different sizes so this variations of sizes elevate RDW.

Complete Blood Count

CBC Without Differential

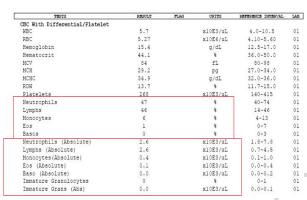
total WBC, not the differential count (Neutrophils, lymphocytes, Monocytes, Eosinophils, and basophils)

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

< 4.5 WBC: leukopenia
>11 WBC leukocytosis



CBC With Differential

Expressed in 2 ways:
- Percentage "from the total WBC"
- Absolute number
Which one is more important? **The absolute count**

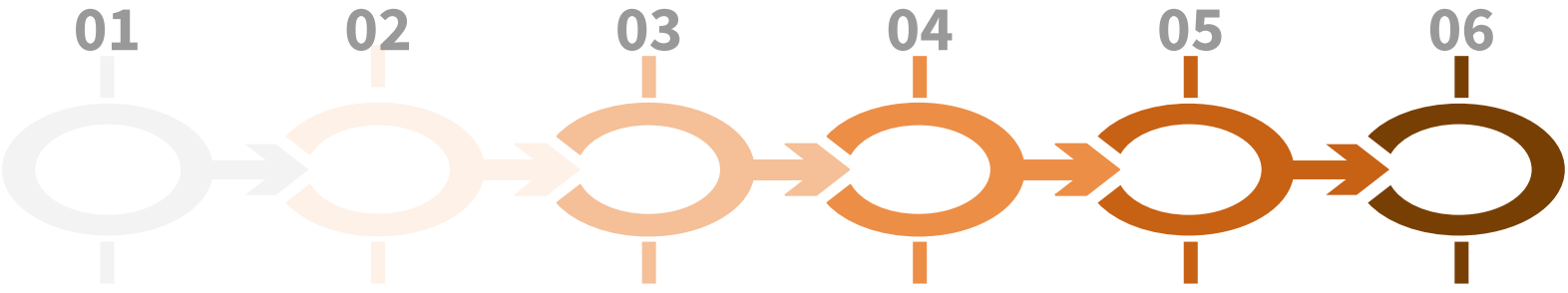
1: If you look here compare to MCH, here you're dividing Hb not by RBC, by hematocrit. So it's similar idea to MCH except that here average amount of Hb in packed RBC compare to the amount of Hb per one RBC. Then you multiply by 100 to get the percentage.

Introduction *(cont.)*

◀ Normal Ranges (adults)

Test	Normal Range	Interpretation
Hemoglobin	Male: 13.5 (14)-17.5 g/dL Female: 11.5 (12.3)-15.3 (15.5) g/dL	**Low:** Anemia **High:** Polycythemia Hb 10 → mild Hb 7-10 → moderate Hb less than 7 → severe
Hematocrit (PCV) The volume of packed RBC in 100 ml blood	Male: 40-50% Female: 36-48%	
RBCs[1]	Male: 4.5-5.9 x10^6/mm3 Female: 4.1-5.1 x10^6/mm3	Measures the absolute RBC count: 1-**Low** 2-**Normal** 3-**High**
MCV	**80-96 IL**	**Low:** Microcytic **Normal:** Normocytic **High:** Macrocytic
MCH	34.4 ± 2.8 pg/RBC	**Low:** Hypochromic **Normal:** Normochromic
MCHC	34.4 ± 1.1 g/dL of RBC	**High:** Hereditary spherocytosis
RDW	**11.5 (11.7)-14.5%**	**High:** Increased: Many types of anemia (**Iron deficiency,** folate deficiency), liver disease
Reticulocytes	0.5-2.5% Males: 1.6 ± 0.5% Females: 1.4 ± 0.5%	
WBC	~4000-11000	**Low:** Leukopenia **High:** Leukocytosis *We are trying to avoid these terminology because they're not specific, you have to look for differential
ESR	2-12 mm/1st hour	

◀ How to read a CBC?



01 Start by WBC

02 Differential "look to the absolute count"

03 RBC components starting by Hb followed by MCV

04 If MCV is normal "normocytic" look at reticulocyte count

05 Then look at RDW

06 Lastly look at platelets count

Introduction *(cont.)*

◀ Leukopenia? Which Cell Line? what degree?

Neutropenia

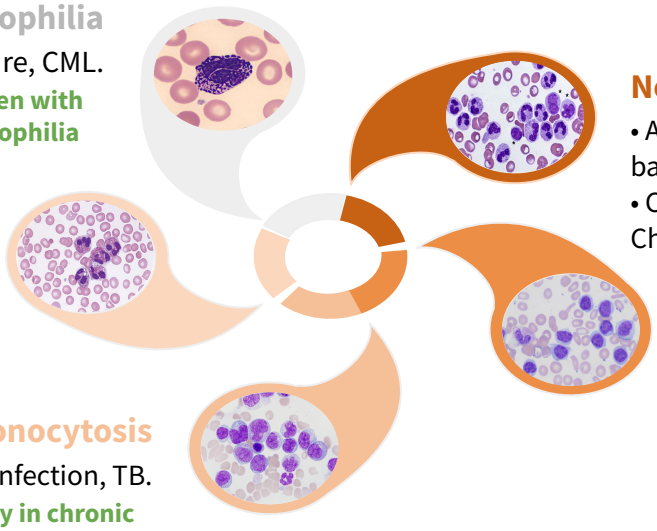
- **Moderate:** ANC: **1-0.5** Risk of infection isn't increased, but need to investigate.
- **Mild:** Absolute Neutrophilic Count (ANC): **1.5-1.** Risk of infection isn't increased, no need to investigate.
- **Severe:** ANC: <**0.5** Risk of infection is increased, must investigate.

◀ Leukocytosis? Which Cell Line?

Basophilia
Very rare, CML.
Happen with neutrophilia

Eosinophilia
Allergic conditions**"asthma"**, parasite, autoimmune diseases and eosinophilic leukemia.

Monocytosis
Fungal infection, TB.
Especially in chronic



Neutrophilia:
• Acute:
bacterial infection, steroids.
• Chronic:
Chronic Myeloid Leukemia (CML).

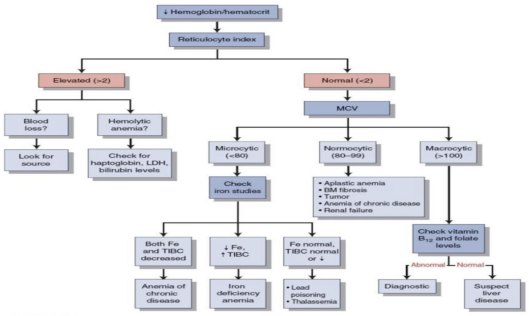
Lymphocytosis
• Acute: viral infections.
• Chronic: Chronic Lymphocytic Leukemia (CLL).
***Look for previous CBC to compare (Acute/Chronic)**

◀ Reticulocyte Count

- Retic count can be reported as an absolute number or as a percentage.
- It's an important initial test in evaluating anemia because it indicates whether effective erythropoiesis is occurring 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 (reticulocytosis) 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.
- Ineffective erythropoiesis: All (any anemia) with normal/low reticulocyte count

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

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



Anemia

➔ Anaemia is present when there is a decrease in Hb in the blood below the reference level for the age and sex of the individual

◀ History

- **Past medical history:** may reveal a disease which is known to be associated with anaemia, such as rheumatoid arthritis (anaemia of chronic disease), or previous surgery (e.g. resection of the stomach or small bowel, which may lead to malabsorption of iron and/or vitamin B12).
- **Drug history:** may reveal the ingestion of drugs which cause blood loss (e.g. aspirin and anti-inflammatory drugs), haemolysis (e.g. sulphonamides) or aplasia (e.g. chloramphenicol).
- FH anemia, diet, melena/hematochezia, malabsorption syndromes, Crohn's disease

◀ Presentation

- Acute or chronic/ Mild, moderate, severe.
  - Patients with gradual onset may be asymptomatic with quite low Hb/HCT
  - Acute onset can cause symptoms with relatively less anemia

Mild anemia:

- few or no symptoms; may be discovered accidentally on lab test

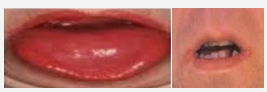
May complain of:

- Fatigue, Low exercise tolerance, SOB, palpitations, lightheadedness on arising
- Sore tongue (glossitis), cracking mouth corners (angular cheilitis), peripheral paraesthesias (numb. toes, etc.)

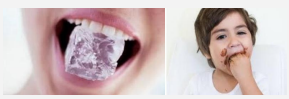
Mild anemia may be "normal" or "OK" for a menstruating woman, but you should always seek a cause in a man or a postmenopausal woman (or child)

◀ Clinical Features

1. Glossitis and Angular stomatitis



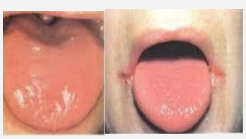
2. **Pica (pagophagia):** Desire to eat mud or ice (In severe iron deficiency)



3. Koilonychia — Spoon like nails, fragile and easily breakable, with iron deficiency anemia

4. **Pallor** (may be jaundiced, think hemolytic)

5. Fatigue and Generalized weakness
6. systolic flow murmur
7. Dyspnea on exertion
8. Ataxia (severe B12/ folate deficiency)
9. Orthostatic lightheadedness Hypotension if acute
10. Decreased vibratory sense/ joint position sense (B12 deficiency, w/ or w/o hematologic changes)
11. Tachycardia, bounding pulses, signs of HF
12. smooth tongue



Anemia

◀ 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:**

1 **The hemoglobin (Hb)**

2 **MCV**

3 **Reticulocyte count (retic count)**

- And the additional required test is the **peripheral blood smear**. **Extremely important.** **Looking for spherocytosis, schistocytes and elliptocytosis.**

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

01 **Low MCV** (MCV <80 fL), also called **microcytic anemia**.

02 **Normal MCV** (MCV **80-100 fL**)[1] with **low retic count**[3], also called **normocytic anemia with inappropriately low bone marrow response.**

03 **Normal MCV** (MCV 80-100 fL) with **high retic count**[2], also called **normocytic anemia with appropriate marrow response.**

04 **High MCV** (MCV >100 fL), also called **macrocytic anemia.**

◀ Ineffective erythropoiesis

➔ **All with normal/low reticulocyte count**

Microcytic
➔ think Fe++ deficiency

Macrocytic
➔ think B12/folate deficiency

Normocytic
➔ think anemia of chronic disease, marrow problems, or other problems

◀ labs

For all:
CBC, reticulocyte count, ± peripheral smear

For some (further workup):
- LDH, Bilirubin
- B12, folate, hemoglobin electrophoresis
- Bone marrow aspirate to assess possible defective hematopoiesis
- Other labs to assess underlying cause and other differential diagnoses (e.g. thyroid function tests, etc.)

1- There are different ranges of MCV in different hospitals, but I want you to remember these numbers "range".
2- Normally if you have anemia, your bone marrow will try to compensate by producing more red blood cells, they produced as reticulocytes "younger RBC", so normal bone marrow will react normally by producing high retic count.
3- This is abnormal, because the bone marrow is not producing more reticulocytes. An inappropriate bone marrow response.

Anemia

★◀ DDx of Anemia

Dr: This is the most important slides "table" in the whole lecture! I want you basically to imprint this in your mind for ever and ever and never forget this

MCV <80fL (TAILS)	MCV N, low retic count	MCV N, high retic count	MCV >100 fL[2]
1. Thalassemia[1] 2. Anemia of inflammation chronic disease[1] 3. Iron deficiency 4. Lead poisoning: Extremely rare 5. Sideroblastic anemia: Congenital, in paediatric	**1.BM failure:** a. Aplastic anemia: **2.BM suppression:** a. Toxins, sepsis b. Organ failure: renal failure, liver failure, adrenal insufficiency c. Chronic inflammation d. Chronic diseases **3.BM infiltration:** a. Lymphoma, leukemia b. Metastatic solid tumors c. Granulomatous disease (e.g.TB)	1. Bleeding 2. Hemolysis 3. Treated nutritional deficiency[3]	1. **Megaloblastic:** (impaired nucleic acid metabolism): a. B12 deficiency b. Folate deficiency c. Drugs: such as methotrexate and HU 2. **Non megaloblastic:** a. Liver disease b. Alcoholism c. Myelodysplasia (MDS) d. Thyroid disease (hypothyroidism)

➔ consider other differentials: Depression: Cardiac (congestive heart failure, aortic stenosis): Pulmonary causes of SOB, Chronic fatigue syndrome, others

Microcytic Anemia

◀ Iron Deficiency Anemia

Iron deficiency is the **most common cause** of anaemia in the world, affecting 30% of the world's population. This is because of the body's limited ability to absorb iron and the frequent loss of iron owing to haemorrhage. Although iron is abundant, most is in the insoluble ferric (Fe3+) form, which has poor bioavailability. Ferrous (Fe2+) is more readily absorbed.

causes

Blood loss

- Most commonly due to chronic bleeding.
- More common in female: **heavy menses**. Iron balance is very close in menstruating women, so iron deficiency is common with no other source of bleeding.
- In males: always investigate for GI causes: occult bleeding, colon cancer, malabsorption, **celiac disease (Most common in KSA)**, etc. Women without heavy menses should also be investigated for GI causes.
- Parasites: A common cause of iron deficiency worldwide is blood loss from the gastrointestinal tract resulting from parasites such as hookworm infestation.

1: The vast majority either iron deficiency or thalassemia
2: How can you know the difference between Megaloblastic and non-megaloblastic anemia?
By doing blood smear looking for hypersegmented neutrophils. Normal neutrophils have 3-5 segment of the nucleus if more called hypersegmented which indicate megaloblastic changes. Also in megaloblastic the RBC looks like oval in shape "ovalocyte", "egg-like". Megaloblastic changes happen because of impaired DNA synthesis.
3: For ex: patient who started as low MCV because of iron deficiency, then he start on iron supplements, MCV went to normal. Or B12 deficiency with high MCV, being treated.

Microcytic Anemia *(cont.)*

◀ Iron Deficiency Anemia *(cont.)*

causes *(cont.)*

02 Increased demand

- Growth
- pregnancy

03 decreased absorption

- Post-gastrectomy, esophageal web.

04 Poor intake

- Dietary, a rare cause.

Diagnosis

Serum iron (Fe)	Measures the concentration of iron in the blood. • Iron will be **low**.
Ferritin level	• Reflects the amount of stored iron. The normal values for serum ferritin are 30–300 µg/L (11.6–144 nmol/L) in males and 15–200 µg/L (5.8–96 nmol/L) in females. • **the most accurate** if it **low**, if it high you have to exclude infection, because it's elevated in inflammation and infections (Ferritin levels can be raised in liver disease and in the acute phase response; in these conditions, a ferritin level of up to 100 µg/L may still be compatible with low bone marrow iron stores). • It is a very specific test; a subnormal level is due to iron deficiency or, very rarely, hypothyroidism or vitamin C deficiency.
Transferrin	The main transport protein for iron. • the body produces transferrin in relationship to the need for iron (lowered by malnutrition, liver disease, the acute phase response and nephrotic syndrome, but raised by pregnancy and the oral contraceptive pill). • When iron stores are low, transferrin levels increase and vice versa.
TIBC	• A measure of all the proteins in the blood that are available to bind with iron (including transferrin). • The TIBC test is a good indirect measurement of transferrin, as transferrin is the primary iron-binding capacity. • TIBC will be **high**, since iron stores are not saturating their binding sites on transferrin.
Transferrin saturation	• TSAT is a good marker of iron status. • TSAT < 20% indicates iron deficiency, a TSAT > 50% may indicate iron overload. • TSAT is calculated with: TSAT= (Fe/TIBC) x 100
MCH and MCHC	• Usually both will be **low**.

Microcytosis and hypochromia are hallmarks, but early iron may be normocytic (±hypochromic)

Microcytic Anemia *(cont.)*

◀ Iron Deficiency Anemia *(cont.)*

Treatment

01 Oral iron replacement ★

- in most cases, ferrous sulphate 200mg (325mg) 2-3 time a day (best preparation), or switch to ferrous gluconate 300mg twice a day if patient has side effects
- All forms of iron are constipating; the amount of constipation directly relates to the amount of elemental iron delivered

02 parenteral iron replacement

- In cases of malabsorption, intolerance to oral iron, or chronic diseases (e.g. IBD).
- given by slow intravenous infusion of low-molecular-weight iron dextran, iron sucrose, ferric carboxymaltose, iron isomaltoside 1000; oral iron should be discontinued.

03 Blood transfusion

- If severe: Hb <7 g/dL, or Hb<10 g/dL with comorbidities (e.g. HF), or the patient requires increased oxygen-carrying capacity (cardiopulmonary disease or CAD).

Follow up the cause of the iron deficiency!

◀ Anemia of chronic disease

Etiology

- Chronic infection (e.g. tuberculosis)
- Malignant diseases
- inflammation (e.g. rheumatoid arthritis, systemic lupus erythematosus [SLE], polymyalgia rheumatica)
- Renal failure (erythropoietin from kidneys)
- Endocrine (e.g. hypothyroid)
- Hepatic disease

Pathophysiology

The exact mechanisms responsible for these effects are not clear but it seems likely that high levels of hepcidin expression play a key role. Cytokines released by inflammatory cells cause macrophages to accumulate iron and not transfer it to plasma or developing red cells (iron block anemia)

Diagnosis

- **Low** serum iron but they are not deficient and don't need iron replacement, the defect is in the transportation
- **Low** TIBC/serum transferrin
- Transferrin saturation is normal or low normal.
- normal or raised serum ferritin → Ferritin reflect the iron storage reticuloendothelial system.
- Bone marrow suppression (EPO is elevated)

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

Treatment

- Correct or manage underlying disease when possible
- EPO (Recombinant erythropoietin therapy) is the treatment of choice for anemia of renal failure and occasionally in inflammatory disease (rheumatoid arthritis, inflammatory bowel disease).
- In bone marrow deficiency/malignancy, treat if possible,
- remove precipitating drugs (immunotherapy, Abx, tissue factors therapy causing severe bone marrow suppression), may require BMT

Microcytic Anemia *(cont.)*

◀ Sideroblastic anemia

Etiology

1. Inherited: as an X-linked disease transmitted by females → leading to a structural defect in δ-aminolaevulinic acid (ALA) synthase.
2. Acquired: myelodysplasia, myeloproliferative disorders, myeloid leukaemia, drugs (e.g. isoniazid), alcohol misuse and lead toxicity. can also occur in other disorders such as rheumatoid arthritis, carcinomas, megaloblastic and haemolytic anaemias.

Diagnosis

- refractory anaemia, a variable number of hypochromic cells in the peripheral blood
- Excess iron and **ring sideroblasts** in the bone marrow (he presence of ring sideroblasts is the diagnostic feature of sideroblastic anaemia).

Treatment

- Pyridoxine: In occasional cases
- Folic acid: may be required to treat accompanying folate deficiency.

◀ DDx of microcytic anemia

➔ The presence of anaemia with microcytosis and hypochromia does not necessarily indicate iron deficiency. The most common other causes are thalassaemia, sideroblastic anaemia and anaemia of chronic disease, and in these disorders the iron stores are normal or increased.

Table 8.3 Microcytic anaemia: the differential diagnosis

	Iron deficiency	Anaemia of chronic disease	Thalassaemia trait (α or β)	Sideroblastic anaemia
MCV	Reduced	Low normal or normal	Very low for degree of anaemia	Low in inherited type but often raised in acquired type
Serum iron	Reduced	Reduced	Normal	Raised
Serum TIBC	Raised	Reduced	Normal	Normal
Serum ferritin	Reduced	Normal or raised	Normal	Raised
Serum soluble transfer receptors	Increased	Normal	Normal or raised	Normal or raised
Iron in marrow	Absent	Present	Present	Present
Iron in erythroblasts	Absent	Absent or reduced	Present	Ring forms

TIBC, total iron binding capacity.

◀ Iron Deficiency vs Thalassemia

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

	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

Introduction

Normocytic, normochromic anaemia is seen in anaemia of chronic disease, in some endocrine disorders (e.g. hypopituitarism, hypothyroidism and hypoadrenalism) and in some haematological disorders (e.g. **aplastic anaemia** and some haemolytic anaemias). In addition, this type of anaemia is seen acutely following blood loss.

Peripheral causes of anemia

→ Anemia is caused by either ineffective erythropoiesis or peripheral causes:

1. **Increased reticulocytes count**
2. **Acute blood loss**
   Very acutely, with hypovolemia, may have normal blood counts, will become anemic with volume replenishment
3. **Hemolytic anemias**

Normocytic Anemia: haemolytic anemias

Definition

Haemolytic anaemias are caused by increased destruction of red cells. The red cell normally survives about 120 days, but in haemolytic anaemias the red cell survival times are considerably shortened.Any condition which leads to a reduction in the mean lifespan of the red cell is a haemolytic disorder. Breakdown of normal red cells occurs in the macrophages of the bone marrow, liver and spleen.

Classification

01

Hemolytic anemias are classified based on cause as follows

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

Immune:
- Autoimmune (warm, cold)
- Alloimmune (haemolytic transduction reaction, Haemolytic disease of newborn, after allogeneic bone marrow or organ transplant)
- drug induced

Non-immune:
- Acquired membrane defect (paroxysmal nocturnal haemoglobinuria)
- Mechanical (microangiopathic, valve prosthesis, march haematouria
- 2ndry to systemic disease (renal or liver failure)

Medications, burns, toxins (e.g. snake venoms, brown recluse spider bite), infections (e.g. malaria, clostridium, plasmodia), Hyperslenism

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

Hemoglobin abnormality (e.g. sickle cell anemia, hemoglobin C disease, thalassemia)

RBCs Membrane defects (e.g. hereditary spherocytosis (discussed in page 2), hereditary elliptocytosis (discussed in page 3) , PNH)

Enzyminopathies (e.g. glucose-6-phosphate dehydrogenase [G6PD] deficiency, pyruvate kinase deficiency, pyrimidine kinase deficiency)

HEMOLYTIC FACIES- CHIPMUNK FACIES

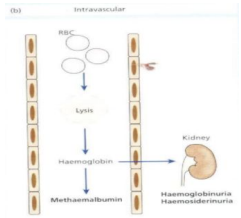
◀ Classification *(cont.)*

02

According to the site

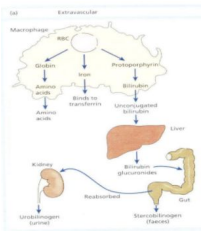
Intravascular haemolysis

When red cells are rapidly destroyed within the circulation → excess free haemoglobin → breakdown & deposit in the cells as hemosiderin (can be detected in the spun sediment of urine using Perls' reaction.), Some of the free plasma haemoglobin is oxidized to methaemoglobin, which dissociates into ferrihaem and globin



Extravascular haemolysis

In most haemolytic conditions red cell destruction is extravascular. within the reticuloendothelial system (macrophages of the RES, particularly the spleen) & excreted by the gut or the kidneys



◀ How to differentiate between haemolytic anemia and anemia due to acute blood loss? ★

By clinical or laboratory findings, these 3 are haemolytic marker (high LDH and indirect bilirubin, low haptoglobin) why low haptoglobin? Because when you have intravascular hemolysis, Hb become in the serum "free", and haptoglobin is within the red blood cells which will be destroyed, Hb will binds to haptoglobin which was produced by liver and go to the kidney to be extracted

	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

◀ Evidence for haemolysis

1 **Shortened RBCs lifespan**

Estimated from 51Cr-labelled RBCs (rarely used)

2 **Intravascular haemolysis**

Suggested by raised levels of plasma haemoglobin, haemosiderinuria, very low or absent haptoglobins, and the presence of methaemalbumin (positive Schumm's test).

Normocytic Anemia: haemolytic anemias *(cont.)*

◀ Diagnosis of haemolytic anemias

01 **Low Hb/Hct**

02 **Elevated reticulocyte count** —due to increased RBC production

03 **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

04 **Low haptoglobin** (especially with intravascular hemolysis)—haptoglobin binds to free Hb, so decreased levels suggest hemoglobin release secondary to RBC destruction

05 **Elevated LDH**—released when RBCs are destroyed

06 **Elevated indirect (unconjugated) bilirubin**—due to degradation of heme as RBCs are destroyed

◀ Treatment of haemolytic anemias

1. Withdraw offending drug (PCN, quinidine, quinine, rifampin, others)
2. Steroids to reduces immune function
3. Last option: Splenectomy because of RBC sequestration, (RBC with antibodies are recognized by the spleen as foreign bodies thus destructed)
4. Treatment of acute bleeding: **Hb less than 7→ transfusion**

Now, some causes of haemolytic anemia will be discussed further:

First: Autoimmune hemolytic anemia

Definition

Autoimmune haemolytic anaemias (AIHA) are acquired disorders resulting from increased red cell destruction due to red cell autoantibodies.

- IgG or IgM labeled as “warm” or “cold” respectively.
  - Antibodies on RBC result in hemolysis
- Usually acute, often with jaundice
- May be drug-induced (e.g. anti-convulsant, and Abx)
- Cold hemolytic anemia often post-infectious (e.g. pneumonia), generally not severe, worsens with exposure of periphery to cold temperatures

Diagnosis: Coomb’s test

- Detects presence of either antibody on RBC .
- Helpful in determining if a hemolytic anemia is immune-mediated

Treatment

- Withdraw offending drug (PCN, quinidine, quinine, rifampin, others)
- **Steroids**/splenectomy– reduces immune function and RBC sequestration, respectively.
- Treatment with anti-CD20 (rituximab) has been successful in some cases.
- Blood transfusion may be necessary, and if so, patient with “cold” autoimmune haemolytic anemia should be placed in a warm environment.

Second: G6PD deficiency

◀ Pathogenesis

Lack of RBC enzyme makes cells very sensitive to oxidative stress (infection, certain drugs) → The enzyme G6PD holds a vital position in the hexose monophosphate shunt, oxidizing glucose-6-phosphate to 6-phosphoglycerate with the reduction of NADP to NADPH. The reaction is necessary in red cells where it is the only source of NADPH, which is used via glutathione to protect the red cell from oxidative damage.

➔ More common in African (less severe) and Mediterranean (severe) populations

◀ Clinical syndromes

Acute drug induced haemolysis → **Favism** → **Chronic haemolytic anemia** → **Neonatal jaundice**

- dose-related

➔ Infections and acute illnesses will also precipitate haemolysis in patients with G6PD deficiency.

Table 8.13 Drugs causing haemolysis in glucose-6-phosphate deficiency

Analgesics, such as:
- Aspirin
- Phenacetin (withdrawn in the UK)

Antimalarials, such as:
- Primaquine
- Pyrimethamine
- Quinine
- Chloroquine
- Pamaquin

Antibacterials, such as:
- Most sulphonamides
- Nitrofurantoin
- Chloramphenicol
- Quinolones

Miscellaneous drugs, such as:
- Dapsone
- Vitamin K
- Probenecid
- Quinidine
- Dimercaprol
- Phenylhydrazine
- Methylene blue

◀ Investigations

1. **blood count:**
   a. Normal between attacks
   b. During attack: may show irregularly contracted cells, bite cells, blister cells, Heinz bodies and reticulocytosis. Haemolysis is evidant
2. G6BD deficiency can be detected using different screening tests:
   a. decreased ability of G6PD-deficient cells to reduce dyes.
   b. The level of the enzyme may also be directly assayed.

Diagnostic problems:

- the screening tests may be normal immediately after an attack (because the oldest red cells with least 6GPD activity are destroyed selectively).
- The diagnosis of heterozygous females may be difficult because the enzyme level may range from very low to normal depending on **lyonization.**

◀ Treatment

No treatment is there but the patient should:

01 avoid triggers (e.g. eating legumes) if possible, especially inciting drugs

02 Underlying infection should be treated.

03 Blood transfusion may be life-saving.

04 Splenectomy is not usually helpful.

Third: Sickle syndromes

Sickle cell haemoglobin (HbS) results from a single-base mutation of adenine to thymine, which produces a substitution of valine for glutamic acid at the sixth codon of the β-globin chain.

◀ Sickle cell disease

1

Worldwide, sickle cell anemia is caused by one of the most common **autosomal recessive gene defects.**

2

The specific Sickle cell mutation is **substitution of hydrophobic valine for glutamic acid at position 6 of the beta-chain**, reducing its solubility under deoxygenated conditions

3

Sickle cell anemia is the most common familial hemolytic anemia[1]

Pathogenesis

- Normal hemoglobin are tetramers composed of two pairs of similar chains
- In Hb electrophoresis: the normal adult red cell contains 96% HbA (α2β2), 3% HbA2 (α2δ2), and 1% fetal Hb (HbF, α2γ2).
- In patients with sickle cell anemia, HbA is absent and completely replaced by HbS, whereas in heterozygous carriers, only about half is replaced (HbS is 70-90%, HbA is zero)

Clinical features

1

Anemia

Chronic haemolysis produces a stable haemoglobin level, usually in the 60–80 g/L range, but an acute fall in the haemoglobin level can occur owing to:

- Splenic sequestration
- **Bone marrow aplasia:** This most commonly occurs following infection with erythrovirus B19, which invades proliferating erythroid progenitors. Leads to loss of reticulocytes in the peripheral blood, because of the failure of erythropoiesis in the marrow.
- Further haemolysis due to drugs, acute infection or associated G6PD deficiency.

2

Spleen

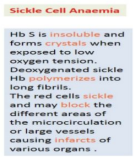
- Abnormal hemoglobin causes change in RBC shape, resulting in constant RBC destruction by the spleen, functional asplenia, susceptible to infection
- **Splenic sequestration:** Vaso-occlusion produces an acute painful enlargement of the spleen. There is splenic pooling of red cells and hypovolaemia, leading in some to circulatory collapse and death.
- **multiple infarctions:** eventually leads to a fibrotic non- functioning spleen.

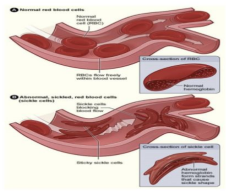
1: This is why it's part of the premarital testing here in KSA, as measure to prevent the severe forms of this disease

Third: Sickle syndromes *(cont.)*

3 Vascular features

- **Arterial occlusion:** leads to infarcts, pain crises, acute chest syndrome, stroke, MI, retinal and renal problems
  - When there are stress factors or deoxygenation, Hb polymerization will occur, and it not caught early will lead to irreversible sickled cells, that causes infarction and acute vascular necrosis (young patient present with MI and stroke)
- **Pulmonary hypertension:** occurring in 30–40% of patients, and is associated with an increased mortality.





4 Acute chest syndrome

This occurs in up to 30%, and pulmonary hypertension and chronic lung disease are the commonest causes of death in adults with sickle cell disease. The acute chest syndrome is caused by infection, fat embolism from necrotic bone marrow or pulmonary infarction due to sequestration of sickle cells. It comprises:

- shortness of breath
- chest pain
- hypoxia
- new chest X-ray changes due to consolidation.

presentation:

- may be gradual or very rapid, leading to death in a few hours

Management:

- pain relief
- high-flow supplemental oxygen
- antibiotics (cefotaxime and clarithromycin) immediately.
- Exchange transfusion will reduce the amount of HbS to <20% if there is no improvement.
- Ventilation (CPAP) may be necessary.

Complications:

- Infections can be due to Chlamydia and mycoplasma, as well as Streptococcus pneumoniae.

5 Long-term problems

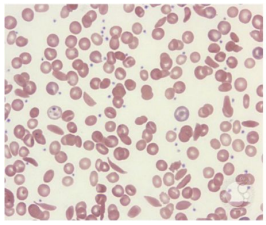
- **Growth and development:** Young children are short but regain their height by adulthood. However, they remain below the normal weight.
- **Bones:** common site for vaso-occlusive episodes, leading to:
  - chronic infarcts.
  - Avascular necrosis of hips and shoulders
  - compression of vertebrae
  - shortening of bones in the hands and feet
  - **Osteomyelitis:** commoner in sickle cell disease and is caused by *Staphylococcus aureus*, *Staph. pneumoniae* and *salmonella.*
- **Infections, leg ulcers, Cholelithiasis, Priapism**
- **cardiac problems:** cardiomegaly, arrhythmias and iron overload cardiomyopathy.
- **Neurological complications:** transient ischaemic attacks, fits, cerebral infarction, cerebral haemorrhage and coma.
- **Liver:** Chronic hepatomegaly and liver dysfunction
- **Renal:** Chronic tubulointerstitial nephritis
- **Eye:** Background retinopathy, proliferative retinopathy, vitreous haemorrhages and retinal detachments
- **Pregnancy:** Impaired placental blood flow causes spontaneous abortion, intrauterine growth retardation, pre-eclampsia and fetal death.

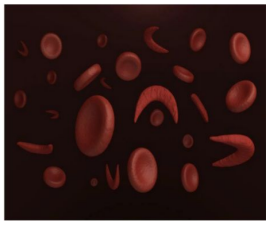
Third: Sickle syndromes *(cont.)*

◀ Sickle cell disease *(cont.)*

BP in SCD

Normally RBC are biconcave, but in SCD they are sickled (crescentic in shape) and they are less soluble and blocking the blood vessels.





Investigations

Blood count: Hb is in the range 60–80 g/L with a high reticulocyte count (10–20%).

01

02

Blood films: can show features of hyposplenism and sickling

Sickle solubility test: A mixture of HbS in a reducing solution such as sodium dithionite gives a turbid appearance because of precipitation of HbS, whereas normal Hb gives a clear solution

03

04

Hb electrophoresis: always needed to confirm the diagnosis. There is **no HbA, 80-95% HbSS and 2–20% HbF.**

Management

- **Keep hydrated:** Acute painful attacks require supportive therapy with intravenous fluids, and adequate analgesia.
- **Treat pain:** Crises can be extremely painful and require strong, usually narcotic, analgesia.
  - **Morphine** is the drug of choice.
  - Milder pain can sometimes be relieved by codeine, paracetamol and NSAIDs
- **Take infection seriously:** Oxygen and antibiotics are only given if specifically indicated.
- **For anemia:** Blood transfusions should only be given for clear indications. Transfusions should be given for:
  - heart failure
  - TIAs
  - Strokes
  - Acute chest syndrome
  - Acute splenic sequestration
  - Aplastic crises.
  - Before elective operations and during pregnancy, repeated transfusions may be used to reduce the proportion of circulating HbS to <20% to prevent sickling
- ***Hydroxycarbamide*** (hydroxyurea): the first drug which has been widely used as therapy for sickle cell anaemia.
- **Inhaled nitric oxide**: a new approach to the treatment of painful crises.
- **Stem cell transplantation**

◀ Sickle cell Trait

- no symptoms unless extreme circumstances cause anoxia, such as flying in non-pressurized aircraft.
- gives some protection against Plasmodium falciparum malaria.
- Typically there is 60% HbA and 40% HbS.
- blood count and film are **normal**.
- **Diagnosis:** made by a positive sickle test or by **Hb electrophoresis.**

Fourth: Thalassemia

◀ General characteristics

- Decreased production of normal hemoglobin polypeptide chains
- Classified according to hemoglobin chain that is affected (α,β,γ,δ)
- Common, variable severity of hemolysis
- Characterized by hypochromic microcytic red cells (MCV markedly decreased while MCHC only slightly decreased)
- can be suspected if electrophoresis shows a compensatory increase in HbA2 and/or F (fetal). (Note: Hb A2 generally does not increase above 10%)

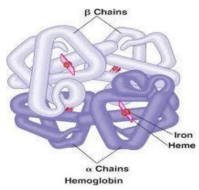
◀ Epidemiology

common in Mediterranean,African, and Asian regions

◀ Pathophysiology

The pathophysiology reflects the impact of an imbalance in the expression of α and β globin chains:

- Normal adult Hb A is composed of 2 alpha and 2 beta chains. In a normal genotype there are two copies of the alpha globin gene on each chromosome 16 (e.g. α α / αα); there is 1 copy of the beta globin gene on each chromosome 11(e.g. β/β).



Hemoglobin types

Hemoglobin Type	Globin Chains
Hb A1—92%	$\alpha_2\beta_2$
Hb A2—2.5%	$\alpha_2\delta_2$
Hb F —<1%	$\alpha_2\gamma_2$
Hb H	β_4
Bart's Hgb	γ_4
Hb S	$\alpha_2\beta_{26}^{glu\rightarrow val}$
Hb C	$\alpha_2\beta_{26}^{glu\rightarrow lys}$

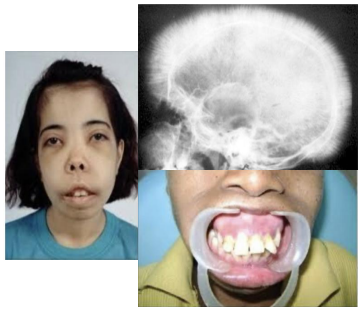
◀ Beta Thalassemia

- **homozygous β-thalassaemia (major):** either no normal β chains are produced (β0) or β-chain production is very reduced (β+). There is an excess of α chains, which precipitate in erythroblasts and red cells causing ineffective erythropoiesis and haemolysis. The excess α chains combine with whatever β, δ and γ chains are produced, resulting in increased quantities of HbA2 and HbF and, at best, small amounts of HbA. They are transfusion dependent, and they get iron overload and complication of it.
  - The inheritance of hereditary persistence of HbF with homozygous β-thalassaemia also results in a milder clinical picture than unmodified β-thalassaemia major because the excess α chains are partially removed by the increased production of γ chains.
- **heterozygous β-thalassaemia:** there is usually symptomless microcytosis with or without mild anaemia (Carrier of the trait "Thalassemia minor" Or "Thalassemia trait": usually they have mild anemia, asymptomatic and don't have complication related to Thalassemia).

◀ Beta Thalassemia *(cont.)*

1 Thalassemia major (Cooley's anemia)

Presentation



- Prominent malar eminence and malalignment of the teeth, secondary to BM hyperplasia.
- Failure to thrive
- Recurrent bacterial infections
- Severe anaemia from 3 to 6 months (when the switch from γ- to β-chain production should normally occur)
- **Extramedullary haemopoiesis** (leads to hepatosplenomegaly and bone expansion → classical thalassaemic facies)
- **Skull X-rays:** shows the characteristic *'hair on end' appearance.*

Management

The aims of treatment are to suppress ineffective erythropoiesis, prevent bony deformities and allow normal activity and development.

- **Long-term folic acid supplements** are required.
- **Regular transfusions**: keep the Hb above 100 g/L. Blood transfusions may be required every 4–6 weeks.
    - If transfusion requirements increase, **splenectomy** may help, although this is usually delayed until after the age of 6 years because of the risk of infection.
        - **Prophylaxis against infection** is required for patients undergoing splenectomy.
    - Iron overload caused by repeated transfusions (transfusion haemosiderosis) may lead to damage to the endocrine glands, liver, pancreas and the myocardium by the time patients reach adolescence.
        - **MRI** (myocardial T2) is useful for monitoring iron overload in thalassaemia
        - The standard iron-chelating agent remains **desferrioxamine**, although it has to be administered parenterally.
        - **Ascorbic acid** 200 mg daily is given, as it increases the urinary excretion of iron in response to desferrioxamine.
- **Bone marrow transplantation**
- **Prenatal diagnosis and gene therap**
- **Patients' partners should be tested**

2 Thalassaemia intermedia

Thalassaemia intermedia includes patients who are symptomatic with **moderate anaemia (Hb 70–100 g/L)**, who do not require regular transfusions.

Presentation

- Thalassaemia intermedia may be due to a combination of homozygous mild β+- and α-thalassaemia, Leading to:
    - reduced α-chain precipitation
    - Less ineffective erythropoiesis
    - Haemolysis.

◀ Beta Thalassemia *(cont.)*

3 Thalassaemia minor (trait)

Presentation

- Asymptomatic.
- Anaemia is mild or absent.
- Hypochromic and microcytic RBCs with a low MCV and MCH (may be confused with iron deficiency.

◀ Alpha Thalassemia

In contrast to β-thalassaemia, α-thalassaemia is often caused by ***gene deletions***, although mutations of the α-globin genes may also occur. The gene for α-globin chains is duplicated on both chromosomes 16, i.e. a normal person has a total of four α-globin genes. Deletion of one α-chain gene (α+) or both α-chain genes (α0) on each chromosome 16 may occur. The former is the most common of these abnormalities.

01 Four-gene deletion

- no α-chain synthesis and only Hb Barts (γ4) is present → Hb Barts cannot carry oxygen and is incompatible with life.
- Infants are either stillborn at 28–40 weeks or die very shortly after birth.

02 Three-gene deletion (HbH disease)

- Has four β chains with low levels of HbA and Hb Barts.
- HbA2 is normal or reduced.
- HbH does not transport oxygen and precipitates in erythroblasts and erythrocytes.
- Features:
  - Moderate anaemia (Hb 70–100 g/L)
  - Splenomegaly (thalassaemia intermedia).
- The patients are not usually transfusion-dependent.

03 Two-gene deletion (α-thalassaemia trait)

- microcytosis with or without mild anaemia.
- HbH bodies may be seen on staining a blood film with brilliant cresyl blue.

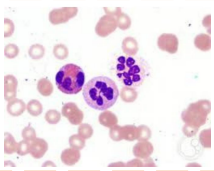
04 One-gene deletion

- blood picture is usually normal.

Macrocytic Anemia

◀ Megaloblastic

Megaloblastic anaemia is characterized by the presence in the bone marrow of erythroblasts with delayed nuclear maturation because of defective DNA synthesis (megaloblasts). macrocytic anemia with ineffective erythropoiesis. Low/normal reticulocyte count, macrocytosis.



◀ Causes

A **B12 deficiency**

B **Folate deficiency**

C **Drugs** (methotrexate, hydroxyurea): because it interferes with DNA metabolism

D **Myelodysplasia due to dyserythropoiesis**

Now, some causes of macrocytic megaloblastic anemia will be discussed further:

First: B12 deficiency

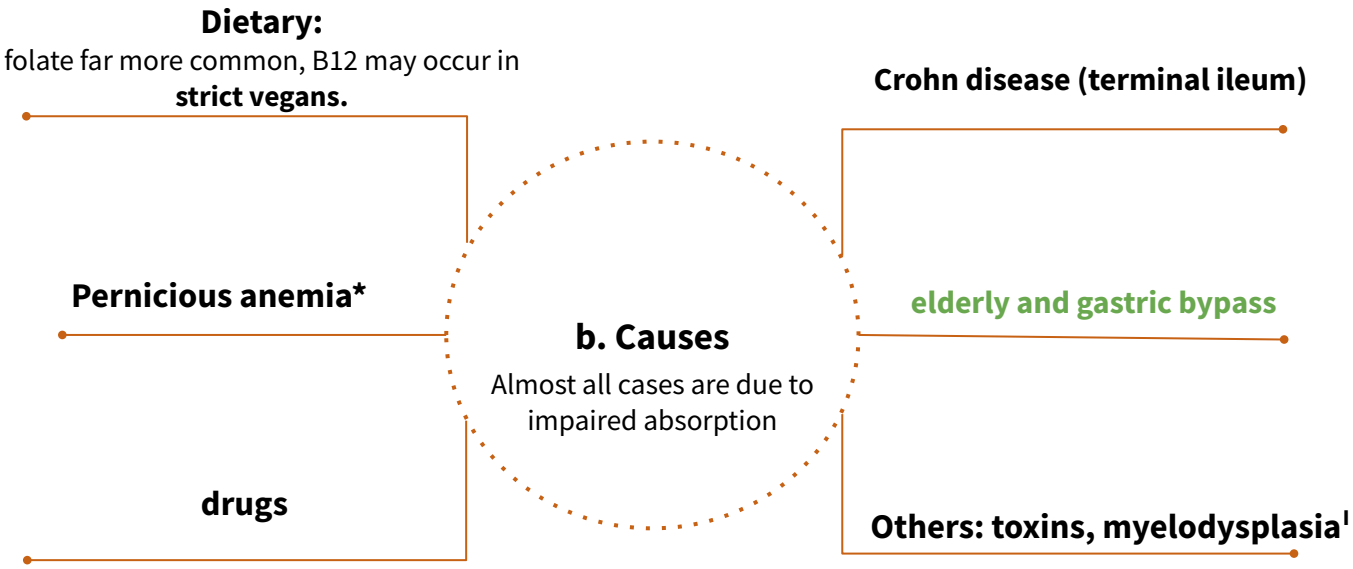
◀ Physiology of vitamin B12

Vitamin B12 needs intrinsic factor for protection from degradation in gut.

- Intrinsic factor is a glycoprotein produced by parietal cells of stomach, It combines with vitamin B12 and protects it through the gut for uptake at terminal ileum.

The main function of B12 is the methylation of homocysteine to methionine with the demethylation of methyl THF polyglutamate to THF. THF is a substrate for folate polyglutamate synthesis.

◀ Causes of vit B12 deficiency



1. High MCV and MCH, but normal B12 and folate → clue to bone marrow diseases rather than deficiencies

First: B12 deficiency *(cont.)*

◀ Causes of vit B12 deficiency *(cont.)*

*Pernicious Anemia

Pathophysiology

Autoimmune attack → atrophic gastritis & loss of parietal cells in the gastric mucosa (the parietal and chief cells are replaced by mucin-secreting cells) → failure of IF production & achlorhydria → to lack of B12 protection in stomach and gut → B12 malabsorption

Investigations

need to test if the IF is deficient:

- **Antibodies against intrinsic factor**
- Anti- parietal cell antibodies, anti-IF antibodies

◀ Clinical features

- Anemia
- lemon-yellow colour (owing to a combination of pallor and mild jaundice caused by excess breakdown of haemoglobin).
- A red sore tongue (glossitis) and angular stomatitis are sometimes present.
- Neurological changes: only with very low levels of serum B12 (<60 ng/L or 50 pmol/L), if left untreated for a long time, can be irreversible. Neurological changes are most commonly associated with B12 deficiency, thus it is part of the tests done in the psychiatry.
  - subacute combined degeneration: polyneuropathy progressively involving the peripheral nerves and the dorsal columns (sensory) and eventually the lateral columns (motor) of the spinal cord
  - symmetrical paraesthesiae in the fingers and toes
  - early loss of vibration sense and proprioception (position sense of joints), and progressive weakness and gait problems → May have positive **Romberg's test**.
  - ataxia and dementia (in severe deficiencies)
  - psychotic problems and hallucinations
  - Optic atrophy

◀ Investigations

1. **Haematological**

   Features of megaloblastic anemia

2. **Bone marrow**

   typical features of megaloblastic erythropoiesis

3. **Serum bilirubin**

   may be raised as a result of ineffective erythropoiesis.

4. **LDH**

   Raised (due to haemolysis)

5. **Serum methylmalonic acid (MMA), homocysteine (HC) and IB**

   Raised

6. **Serum B12**

   usually well below 160 ng/L, which is the lower end of the normal range.

7. **Look for secondary causes**

   Secondary causes of poor absorption should be sought (gastritis, ileal problems e.g Tb ileitis)

8. **Serum folate**

   normal or high

First: B12 deficiency *(cont.)*

◀ Investigations *(cont.)*

9 **Schilling test**

Assesses radioactive B12 absorption, may be useful to establish etiology of B12 deficiency

◀ Treatment

Vitamin B12 deficiency is treated with hydroxocobalamin B12 1000 mg IM for 6 doses 2 or 3 days apart, followed by maintenance therapy of 1000 µg every 3 months for life.

- B12 stores take a long time to deplete; missed doses are not usually a problem
- Oral supplementation is gaining support; usually effective in pernicious anemia (1-2 mg PO QD)
- given IM in malabsorption, and oral in dietary deficiency
- Reticulocyte count should respond in 1 wk, the first to be increased in the not the Hb but rather the reticulocyte count, thus it's the parameter used to assess the response to treatment.

Second: Folate deficiency

◀ Overview

- Folate intake is usually dietary, and may be deficient with low fresh fruit & vegetable intake.
- Cooking causes a loss of 60–90% of the folate.
- The minimal daily requirement is about 100 µg.
- Folate supplementation prevents neural tube defects in pregnancy.
- Folate deficiency is most commonly drug related

◀ Causes

01 **Poor intake:** Old age, Poor social conditions, starvation, alcohol excess (alcohol also causes impared utilization)

02 **gastrointestinal:** partial gastrectomy, coeliac disease, crohn's, cancer

05 **malabsorption:** small bowel disease

03 **Antifolate drugs:** anticonvulsants (phenytoin, primidone), Methotrexate, Pyrimethamine, trimethoprim

04 **Physiological:** pregnancy, lactation, prematurity

06 **Pathological:** Haematological disease with excess RBC production (e.g. haemolysis) malignancy with increased cell turnover, Inflammatory disease, metabolic disease (e.g. homocystinuria, haemo- and peritoneal dialysis)

Second: Folate deficiency *(cont.)*

◀ Clinical features

- Patients with folate deficiency may be asymptomatic or present with symptoms of anaemia or of the underlying cause.
- Glossitis can occur.
- Unlike with B12 deficiency**, neuropathy does not occur.**

◀ Investigations

1. **Serum folate level:** Low (Normal levels of serum folate are 4–18 µg/L (5–63 nmol/L)).

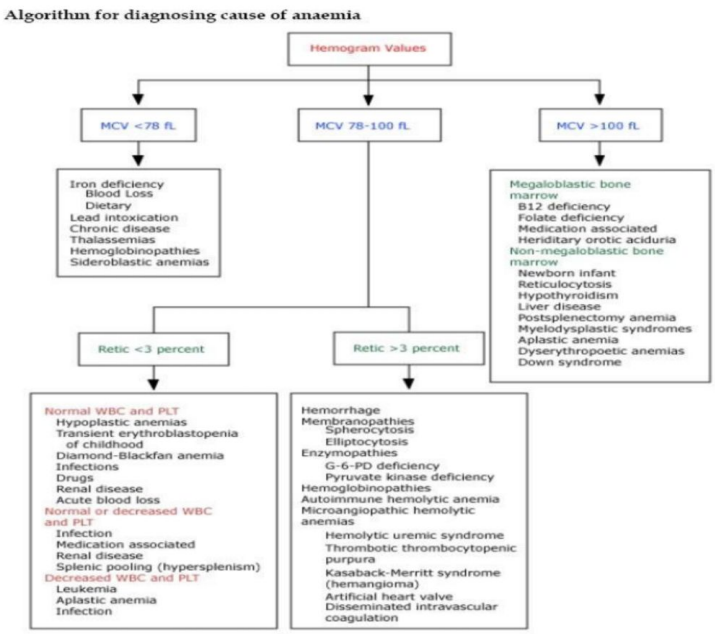
2. **red cell folate level:** The amount of folate in the red cells is a better measure of tissue folate; the normal range is 160–640 µg/L.

◀ Treatment

Daily oral folic acid replacement (Oral folic acid 5 mg daily for 3 weeks will treat acute deficiency and 5 mg once weekly is adequate maintenance therapy).

- Correction of folate deficiency will correct hematologic abnormalities without correcting neurological abnormalities
- Check B12 and correct first
- Prophylactic folic acid in pregnancy prevents megaloblastosis in women at risk, and reduces the risk of fetal neural tube defects.

Algorithm for diagnosing cause of anaemia



Cases

You should read and interpret the CBC at the same time.

- Hb 10 or higher → mild Anemia
- Hb 7-10 → moderate anemia
- Hb less than 7 → severe anemia
- MPV (mean platelet volume) it's similar to MCV, but it's not that important.
  - if it high indicate high large sizes platelets (which may happen in peripheral destruction in someone with thrombocytopenia)

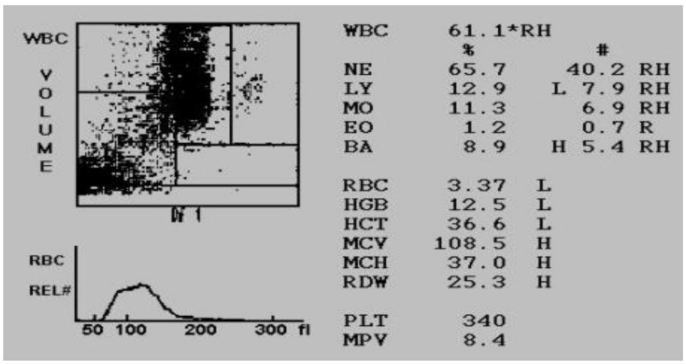
◀ Case study 1

Test	Lo	Hi	Result	Test Information
CBC measurements			The patient's values	Normal Values
* SIGNED OFF by User Id: [redacted] on 15Apr09 at 8:47				
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 high normal, RDW is little high
  - Ferritin is **normal**
- **DDx:** Thalassemia
- Mild microcytic anemia with very low MCV "comparing to Hb which is slightly low"

◀ Case Study 2



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
- **DDx:** (Vitamin B12 or folate deficiency)
- leukocytosis and look at the differential count, the patient have neutrophilia *"then is it Acute or Chronic?"* (Most likely CML), thrombocytopenia, basophilia and normal eosinophils count, Macrocytic anemia, thus do a smear to look for Megaloblastic changes.

◀ Case study 3

Date and Time Collected	Date Entered	Date and Time Reported	Physician Name	MR#	Physician ID
03/09/12 16:51	03/09/12	03/09/12 16:15ET	KLIX, MARY	[redacted]	1669447595

Tests Ordered: CBC With Differential/Platelet

PID: [redacted]

General Comments

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

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Dir: Meyers, James MD
For inquiries, the physician may contact: Branch: 314-453-9648 Lab: 314-453-9648

- **Findings:**
  - Macrocytosis
  - Low platelets
- **DDx:** Bone Marrow disorder (Myelodysplasic syndrome)
- Macrocytosis without anemia, normal Hb and high MCV, you have to do smear to look for Megaloblastic changes.

Cases

◀ Case study 4

- Patient with this CBC findings:
  - Hb 5, MCV 85 (normal)?
  - What's next? **Look for reticulocytes count**
  - Retic count was 300 (3%)**

- **DDx:** Severe anemia, normocytic anemia, High reticulocytes count indicates Healthy Bone Marrow → appropriate response
  1. **Bleeding**
  2. **Hemolysis**
  3. **Treated nutritional deficiency**

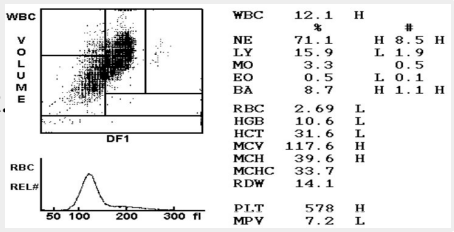
◀ Case study 5

- 17 ys lady presented to the ER with fatigue and exercise intolerance found to have HGB 75gms normal MCV and MCH, platelets, WBCs.

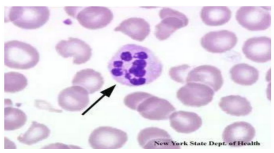
1. **What you will order lab next?** DDx: Autoimmune hemolytic anemia
   - **a.** As NC NC anemia will order hemolytic panel
   - **b.** LDH, bilirubin, Coombs test if hemolysis
     - **i.** LDH 1550, D, Coombs +ve
2. **What you will give her immediate ttt?**
   - **a.** If confirmed AIHA immediate management will be:
     - **i.** Steroids only if no serious findings
     - **ii.** Steroids and blood if serious findings
3. **What is your further workup?**
   - **a.** Search for underlying autoimmune disorders
     - **i.** Result ANA, Anti DsDNA v. high 1:10980
4. **Final Dx :** SLE with 2ry AIHA (because of her age)

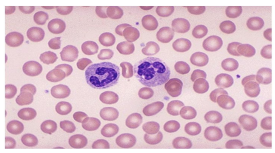
◀ Case study 6

- A 48 year old male has become progressively more fatigued at the end of the day. This has been going on for months. In the past month he has noted paresthesia with numbness in his feet. A CBC demonstrates the findings shown. A peripheral blood smear shows red blood cells displaying macro- ovalocytosis and neutrophils with hypersegmentation.



1. **Which of the following tests would be most useful to determine the etiology?**
   - a. Hemoglobin electrophoresis
   - b. Reticulocyte count
   - c. Stool for occult blood
   - d. Vitamin B12 assay
   - e. Bone marrow biopsy



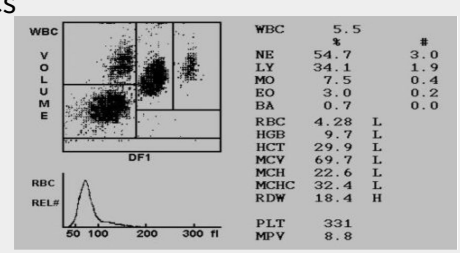


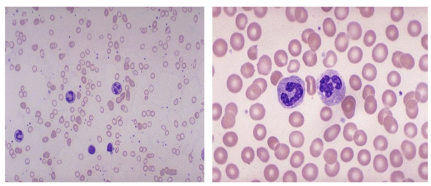
2. **What is the diagnosis from these findings?** This is a macrocytic (megaloblastic) anemia. The neurologic findings suggest vitamin B12 deficiency (pernicious anemia).
3. **How do you explain the neurologic findings?** The B12 deficiency leads to degeneration in the spinal cord (posterior and lateral columns).

Cases

◀ Case study 7

- A 72 year old male has the CBC findings shown. Peripheral RBCs are hypochromic & microcytic.
- **Findings:**
  - **Hb:** low
  - **MCV:** low
  - **RBC count:** low
  - **RDW:** high





1. **What test would you order for this patient?**
   a. Hemoglobin Electrophoresis (iron levels done first)
   b. Retic count
   c. Stool for occult blood (if there is iron is low, ask for it)
   d. B12 Assay (not needed, it's not megaloblastic)
   e. Bone marrow biopsy
   f. Ferritin, Iron, TIBC (before proceeding further)
2. **What is your diagnosis?** Iron Deficiency Anemia
3. **What is the next step for this patient?** Colonoscopy (due to his age, we need to screen for cancer)

◀ Case Study 8

All of the following produce microcytic anemia EXCEPT:
A. Sideroblastic anemia
B. Thalassemia
C. Pernicious anemia (B12 Deficiency)
D. Lead poisoning

◀ Case Study 9

Normocytic normochromic anemia is an expected feature of:
A. B thalassemia
B. Chronic renal failure
C. Iron deficiency anemia
D. Alcoholic liver disease
E. Myelodysplastic syndrome

◀ Case Study 10

Which of the following anemias is associated with splenomegaly?
A. Chronic renal failure
B. Aplastic anemia
C. Hereditary spherocytosis
D. Sickle cell anemia

◀ Case Study 11

Red cell osmotic fragility is increased in:
A. Thalassemia
B. Hereditary spherocytosis
C. Iron deficiency anemia
D. ITP

Summary

Anemia			
Clinical features: pallor - fatigue - weakness - confusion dyspnea on exertion - tachycardia -hypotension **Approach to anemia: CBC(Hb - MCV - Reticulocyte count) + peripheral blood smear**			
Type according to MCV	**Microcytic**	**Normocytic**	**Macrocytic**
Etiology	**Iron deficiency anemia** (most common type) due to: ● Blood loss ● Malabsorption ● Dietary deficiency (rare) **Thalassemia** (inherited disorder due to inadequate production of a or b globin) I. Thalassemia a II. Thalassemia b	**Hemolytic anemia** : ➢ Hereditary or acquired ➢ Intra/Extravascular **Anemia of chronic disease** : ● Chronic infection ● Chronic inflammation ● Cancer	**Megaloblastic** : ● B12 deficiency ● Folate deficiency ● Drug (methotrexate) **Non- megaloblastic** : ● Liver disease,alcohol ● Thyroid disease (hypothyroidism) ● Myelodysplasia(MDS) ● Myeloma ● Congenital bone marrow failure syndrome
Clinical manifestation	**IDA:** ● Signs & symptoms of anemia ● Koilonychia (severe deficiency) ● Glossitis ● Angular stomatitis ● Pica (pagophagia) **Thalassemia:** B -B **Minor**: asymptomatic/mild anemia -B **Intermedia**: intermediate anemia -B **Major**: “crew-cut” appearance,hepatosplenomegaly, growth retardation A -**Silent carrier**: asymptotic -**Trait**: mild anemia -**HB H**: severe anemia -**Deletion of 4**: Hydrops fetalis	1. Sign & symptoms of anemia 2. Signs & symptoms of underlying pathology	● Signs & symptoms of anemia **Megaloblastic :** ● Glossitis ● Stomatitis ● **Neuropathy** (B12 deficiency) ● Loss of position/vibratory sensation in lower extremities, ataxia & upper motor neuron **Non-megaloblastic:** ● Signs & symptoms of underlying pathology

Summary

Diagnosis	**IDA**: • Bone marrow biopsy—gold standard Low ➔ Ferritin level **(Most specific)** ➔ Serum iron (Fe) ➔ Transferrin saturation (TSAT) High ➔ Transferrin ➔ TIBC **Thalassemia**: • Hemoglobin electrophoresis • Peripheral blood smear (target cell / Normo Hypo RBC) **In IDA MCV is low, but in Thalassemia MCV is very low**	**Hemolytic anemia:** Both Intra/Extravascular Low ➔ Hb or Hct High ➔ Reticulocyte ➔ LDL ➔ Unconjugated bilirubin ➔ Urinary bilirubin Intravascular -Low Haptoglobin -High Methemoglobin -Hemoglobinuria **Anemia of chronic disease:** Low ➔ Serum iron ➔ TIBC -High serum ferritin -Normal/low normal Transferrin saturation (TSAT) *it can be Normochromic/Micro*	**Megaloblastic** : Peripheral blood smear • Hyper-segmented neutrophils • Macrocytic R Low ➔ Serum vitamin B12 level High ➔ Serum methylmalonic acid level ➔ Serum homocysteine level • Antibodies against intrinsic factor • Schilling test **Non-megaloblastic**: N/A
Treatment	**IDA**: • Oral iron replacement • Parenteral iron replacement • Blood transfusion **Thalassemia**: B -B **Minor** & **Intermdia**: no need -B **Major**: frequent PRBC transfusion A -A no need except **Hb H**	Treat the underlying pathology -**Don't give iron**	**Megaloblastic**: ➢ B12 deficiency: Parenteral therapy of vitamin B12 (I.M) ➢ Folate deficiency: **Daily oral folic acid replacement** **Non-megaloblastic:** ➢ (MDS) • Supportive(transfusion, GCSF,antibiotics,EPO) • Hypomethylating agents (azacitidine) • Stem cell replacement

Lecture Quiz

Q1: 73 years 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(elevated). What is the most appropriate next step in management ?

A- Vitamin B12 level
B- Folate level
C- peripheral blood smear
D- Schilling test

Q2:A 55 years old man is being evaluated for constipation. There's 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 mg/dL (normal 50 - 150 mg/dL)), iron binding- capacity is 450 mg/dL (normal 250 - 370 mg/dL), saturation is 1% (normal 20% - 45%), and ferritin is 10 mg/L (normal 15- 400 mg/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

Q3:A 43-year-old man with sickle cell disease is admitted with an acute pain crisis. His only routine medication is folic acid. His hematocrit on admission is 34%. On the third hospital day, the hematocrit drops to 22%. What is the best initial test?

A- Reticulocyte count.
B-Peripheral smear. Folate level.
C-Parvovirus B-19 IgM level.
D-Bone marrow.

Q4:A 50 years 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 mg/d, MCV is 80 fL, serum iron is 28 mg/dL, iron binding capacity is 200 mg/dL (normal 250 - 370 mg/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

Q5:A 60 year old man develops numbness of the feet. On physical examination he has lost proprioception in the lower extremities and is noticed to have a wide based gait with a positive Romberg sign. His past medical history includes hypertension, hypothyroidism, and previous gastrectomy for gastric cancer. The peripheral blood smear shows macrocytosis, and neutrophils with 6 to 8 nuclear lobulations. Which one of the following is most likely cause of his symptoms ?

A- Folic acid deficiency
B- Vitamin B12 deficiency
C- Vitamin K deficiency
D- Iron deficiency

Answers: Q1:C | Q2:D | Q3:A | Q4:C | Q5:B

THANKS!!

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Send us your feedback:
We are all ears!