"He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all." – William Osler

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MEDICINE
TEAMWORK

ANEMIA

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Green: doctor's notes Grey: team's notes (mostly explanations)

Introduction

❖ Anemia is present when a patient has a reduced amount of hemoglobin per unit volume of blood when compared with the correct reference population for that patient.

Hemoglobin levels might be different in certain populations, ex. People living in cold areas or people living in high altitudes have higher levels of hemoglobin (because of low oxygen and high erythropoietin production) and this is normal.

- It is the chronic syndrome of highest prevalence in clinical medicine. (30% of the world is anemic)

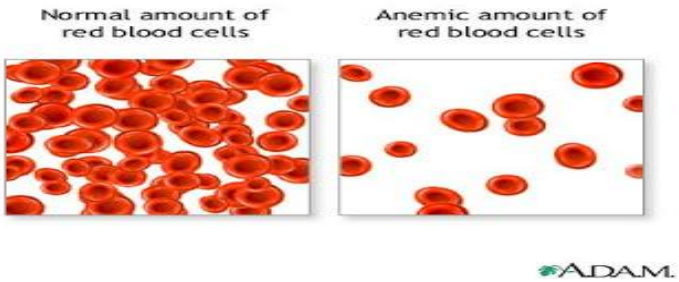
❖ The World Health Organization **(WHO) defines anemia generally as:-**

A hematocrit (PCV) of: **<40%** (hemoglobin **<13.0** g/dL) in men or

<37% (hemoglobin **<12.0** g/dL) in women.

Complete Blood Count		
	Normal value	note
Hb conc.	**Males: 13 – 17 g/dl** **Females: 12 – 16 g/dl**	• it's the first thing we look at • if low, look at MCV and reticulocytes to know the type of anemia (page 4)
MCV	**80 – 94 fl** (or 87±7)	• (mean corpuscular volume) Defines the size of the RBCs • Femtoliter (fl) = 1x 10^{-15} liter
Reticulocyte count	0.5% - 2% (20,000 – 100,000 /mm^3)	• An erythrocyte newly released from the bone marrow • Young red cell, bigger in size, gives high MCV
Hematocrit (PCV)	Male: 40% - 54% Female: 37% - 47%	• Packed cell volume (cellular part of the blood) • It's 3 times the hemoglobin ex. If Hb= 15, then PCV= 45
RDW	11% - 15% (Red cell Distribution Width)	• Measure of red cell size variability • If low, means RBCs are almost the same size (normal)
MCH	29 ± 2 pg	• (mean corpuscular Hb) Quantifies the amount of Hb per RBC, in picograms (pg) per cell
MCHC	34 ± 2 g/dl	• (mean corpuscular Hb content) Indicates the amount of Hb per unit volume (correlates Hb content with the volume of the cell)
RBC count	Male: 4.5 - 6.5 x10^{12}/L Female: 3.8 - 5.8 x10^{12}/L	• It's usually low in anemia, but could be normal or high, ex. Thalassemia trait
WBC count	3.5 - 10.5 x 10^9/L	
Platelet count	150 – 350 x10^9/L	

- In any patient's CBC, the main 3 things we look at are the Hb, WBCs and platelets. (Hb, MCV and reticulocytes are the most important in anemia)
- It's important to know the normal values of Hb and MCV



- Despite having a set of peculiar symptoms and signs, anemia is not a disease per se, but a syndrome, as it may arise from an extensive list of causes.

It can be from either:

- A Single cell line (RBC) problem (most common)
- Or Multiple cell line problem (RBC, WBC, Platelet) all are affected, from either:

- Bone marrow suppression/failure (ex. Leukemia, some drugs, myelofibrosis, aplastic anemia)
- Immunologic disorders (ex. SLE)
- Peripheral destruction/sequestration (separation by large spleen, like in chronic liver disease)

Symptoms of Anemia: (in general)

- ✓ General malaise, weakness, fatigue, breathlessness on exertion, palpitations, dizziness, angina. (angina in older patients who have underlying ischemic heart disease)
- ✓ Desire to eat sand and clay. (Common in severe iron deficiency anemia, especially in females. Reason is unknown)
- ✓ Menorrhagia is common in women.
- The central nervous system, the heart and the muscle mass are the most affected organs, since they are the ones that most need oxygen for their functions.
- The symptoms increase with physical activity, as this consumes oxygen.

Relation between Hb levels and symptoms: (symptoms might overlap, and it depends on the age and condition)

Hemogobin level	Symptoms	notes
between 9 - 11 g/dL	(mild symptoms)	there's irritability and headache; in the elderly fatigability is observed, and angina may occur.
between 6 - 9 g/dL	(moderate symptoms)	there's tachycardia, dyspnea and fatigue upon mild effort.
below 6 g/dL	(severe symptoms)	symptoms are present even on sedentary activities
below 3.5 g/dL		heart failure is impending and any activity is difficult. (because the heart reaches a level where it can no longer keep up with the body's oxygen demand)

- Symptoms depend on the duration on which Hb is lost, for example: if there was acute blood loss or bleed → symptoms would be severe, but if the loss was over a long period of time → symptoms would be mild, because the body would have time to compensate.

Anemia can be either acute or chronic: (The Dr. only mentioned the underlined)

- In acute anemia (sudden loss of blood), the lack of blood volume in the circulatory system is more important than the deficiency of hemoglobin. A loss up to 10% of blood volume, as that taking place upon blood donation, is well tolerated. Losses between 10 and 20% cause postural hypotension, dizziness and faint. In losses above 20%, there's tachycardia, cold extremities, extreme paleness and hypotension, followed by shock; should the loss surmount 30%, without immediate replacement of intravenous fluids, the shock rapidly becomes irreversible and fatal.
- In chronic anemia, symptoms are less, there's no decrease in blood volume, which is compensated by an increase in plasma volume.

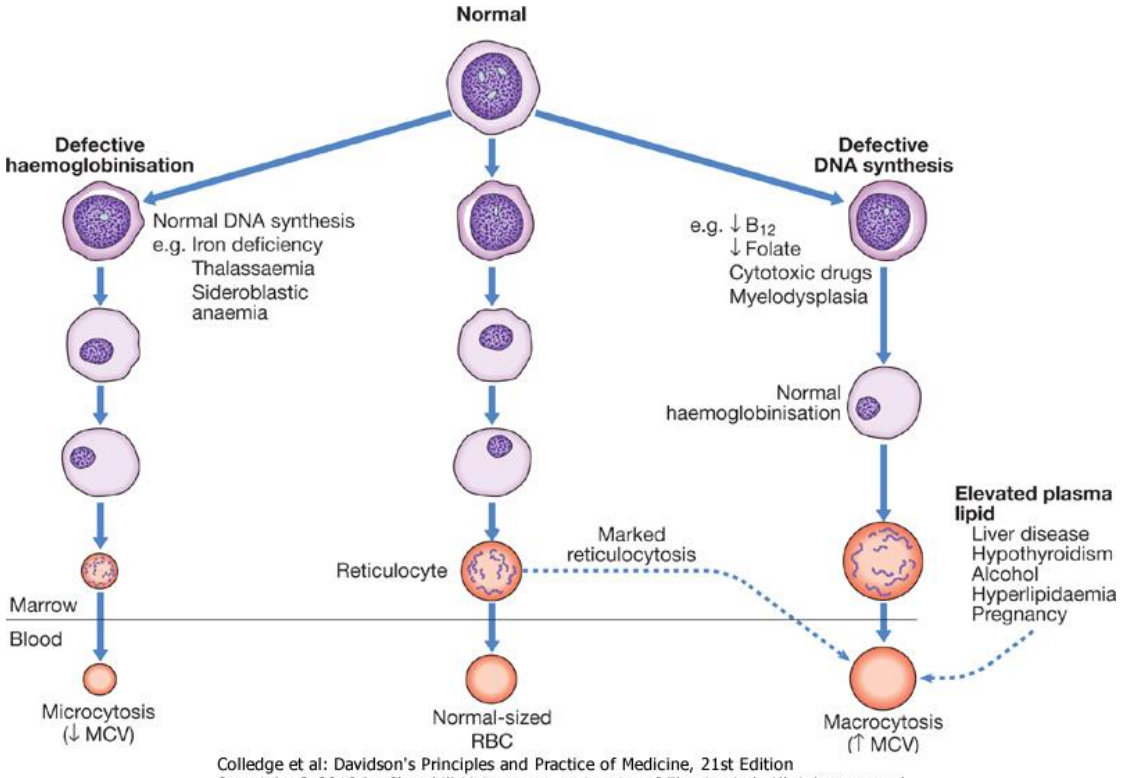
Classification of Anemia:

(the real lecture starts in this page ☺)

By pathophysiology (based on underlying process)**:**

- Blood loss
- Deficiency of nutrients
- Increased destruction (Hemolysis)
- Decreased/Failure of production (Bone marrow failure)

By morphology (by MCV) **Important:** (the image is just an explanation)



(1) MCV < 80 fl. **Microcytic Hypochromic**	**(2)** MCV= 80 – 94 fl. **Normocytic Normochromic**	**(3)** MCV > 94 fl. **Macrocytic Hyperchromic**
a) Iron deficiency anemia **b) thalassemia** c) sideroblastic anemia & lead poisoning	**a) Anemia of chronic disease** (could also be microcytic) **b) hemolytic anemia** **c) aplastic anemia** d) blood loss (recent)	**a) Megaloblastic:** • **B12 deficiency/Folate deficiency** (MCV mostly >120 fl.) **b) Non megaloblastic:** • Myelodysplastic syndrome • liver disease • alcohol • hypothyroidism • cytotoxic drugs

- In general, All of them have low levels of reticulocytes, EXCEPT in hemolytic anemia/recent blood loss, where levels are high. (retic. count ↓ in production problems, ↑ survival/destruction problems)
- Hypochromia: pale red cells, always accompanied by microcytosis.

(The rest of the lecture is based on this classification)

(1) Microcytic Anemia

Explanation: Red cells in the bone marrow must acquire a minimum level of haemoglobin before being released into the blood stream. Whilst in the marrow compartment, red cell precursors undergo cell division driven by erythropoietin. 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. The MCV is low because component parts of the haemoglobin molecule are not fully available: that is, iron in iron deficiency, globin chains in thalassaemia, haem ring in congenital sideroblastic anaemia and, occasionally, poor iron utilisation in the anaemia of chronic disease.

a) Iron deficiency anemia: MCV mostly <70

Case example: 60 year old male presents with fatigue and paleness. His CBC showed Low MCV and MCH and Hb=9 . He's known to have gastritis and a duodenal ulcer. What is the most likely diagnosis?

❖ Iron deficiency anemia **(IDA)**: It is a condition when supply of iron in the body to bone marrow falls short of that required for the production of red blood cells. (iron losses or physiological requirements exceed absorption) (very common in young females)

- It is the most common cause of anemia throughout the world. (about half anemic patients)
- Iron deficiency related to inadequate replacement of lost iron is the most frequent cause of asymptomatic anemia and has a variety of causes.

▪ Daily iron requirements:
  - men and postmenopausal women: 0.5 and 1 mg
  - Menstruating and pregnant women: 2 and 2.5 mg, respectively.
    - Max. absorption: 4 mg/day. Max. excretion: 2-3 mg/day.

(Iron metabolism is tightly regulated in the body, it's not possible to absorb or excrete more than this, whether you have a deficiency or an overload. This is because most of the body's iron is recycled)

  - Food rich in iron include red meat, liver, etc…

❖ **Causes** of IDA:

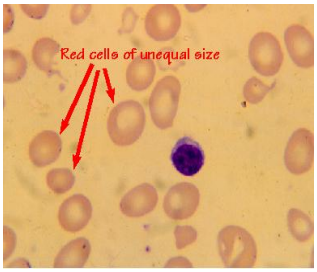
1- Blood loss (chronic)	• Most common cause of iron deficiency anemia in adults ✓ Men and postmenopausal women → GI loss most common ✓ Premenopausal (child-bearing) women → menstruation, then GI
2- decreased iron absorption	• Due to disorder of the digestive system (Iron is absorbed actively in the upper small intestine and hence can be affected by celiac disease)
3- increased physiological demands	• example: Increased physical activity, growing children • pregnancy, parturition and lactation **(IDA is very common in pregnancy)** During pregnancy there's increased demand of iron & folate, they're Hb drops because of plasma expansion • Inadequate dietary intake

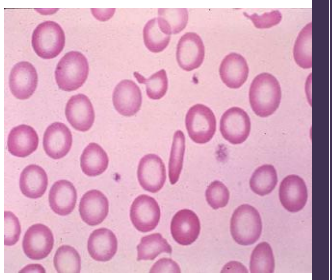
➢ Because men and postmenopausal women rarely develop iron deficiency that is not related to gastrointestinal blood loss (often occult), an evaluation of gastrointestinal tract (ex. colonoscopy) must be performed when an iron deficiency is detected in these individuals. (especially in the elderly, you must rule out colon cancer)

Causes of GI blood loss: Peptic ulcer, piles, hiatus hernia, carcinoma of stomach, carcinoma colon, chronic ingestion of a certain type of pain relievers, hookworm infestation…etc

❖ **Diagnosis:**

- **Peripheral blood smear:**
  - shows pale small cells. (microcytic hypochromic)
  - Aniso-poikilocytosis





Anisocytosis: red cells of unequal size. Reflected in increased RDW. Poikilocytosis: traditional term for red cells of unequal shape (in the blood smear on the right there's a pencil shaped RBC)

- koilonychia
- **Iron study:**

Serum iron	Serum ferritin	TIBC	RDW
↓	↓	↑	↑

Ferritin: the cellular storage protein for iron. (We measure it to assess the body's iron stores)
Total iron binding capacity (TIBC): the measurement of the blood's capacity to bind iron with transferrin (the iron transporter). When it's high, it means that there's a lot of unbound or free transferrin, because of low levels of iron.
(MVC might be normal in cases such as IDA with B12 anemia, but **RDW** would still be high)

❖ **Treatment:** (replace iron)

- Correction of iron deficiency – to restore Hb levels and replenish iron stores.
- ✓ **Oral iron** administration is advised. (Ferrous sulfate)
  - But it has side effects, ex. constipation, nausea, abdominal pain, also 98% of it goes to stool causing black stools. (So it's quite unpleasant)
- ✓ Parenteral iron may be needed occasionally. (like if the patient doesn't tolerate oral)
- ✓ Blood transfusion in severe anemia.
- ✓ Treat the underlying cause.

b) Thalassemia:

MCV mostly <70

- Very common, inherited disease. (especially in the Mediterranean)

❖ The normal Hb is a tetramer of 2 alpha and 2 beta chains (2 α 2β), but in thalassemia there's a partial or complete failure in the synthesis of one of those chains.

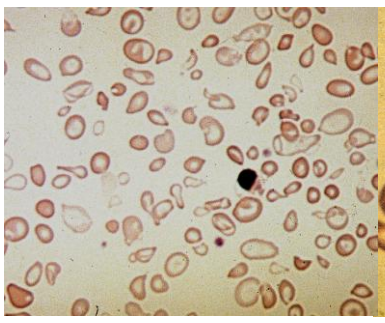
	HbA (2 α 2β)	**HbF** (2 α 2γ)	**HbA_2** (2 α 2δ)
Adult	~94–96%	~1%	~1-3%
New-born	~10-30%	~70-80%	~0%

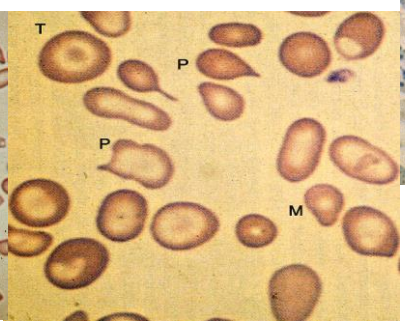
❖ Types of thalassemia:

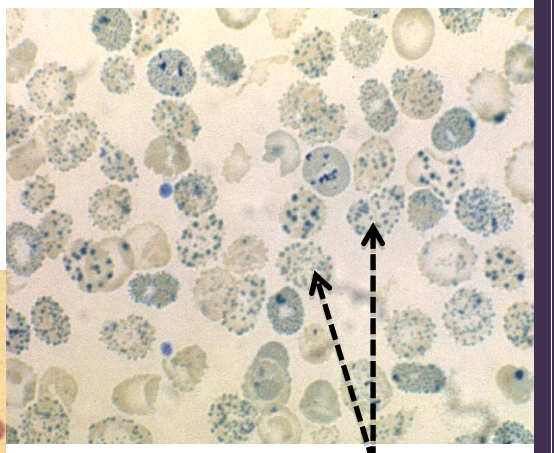
α - thalassemia	β - thalassemia
➢ Decrease or total lack of α globin synthesis	➢ Decrease or total lack of β globin synthesis
Pathogenesis	
• Decrease in α chains, which are a component of all types of Hb. • β chains form tetramers (4β, also known as HbH), which are abnormal and functionally useless. • The severity depends on the rate of reduction in α chain synthesis or deleted gene loci.	• Caused by a gene mutation for the β globin chain (chromosome 11). • Underproduction of β chains leads to an excess of normally produced α chains. • These normal chains are unstable, precipitate and cause hemolysis of the affected RBCs.
Classification	
If 1 α loci deleted (Genotype – α / α α): 1. Silent carrier (or mild trait) ✓ Normal or mildly decreased Hb.	1. Silent carrier ✓ Normal or mildly decreased Hb.
If 2 α loci deleted(Genotype ––/ α α OR– α /– α): 2. Thalassemia trait (or minor) ✓ Mild microcytic hypochromic anemia (Hb 9-10)	2. Thalassemia trait (or minor). (heterozygous) ✓ Mild microcytic hypochromic anemia (Hb 9-10) ✓ Hb electrophoresis shows elevated HbF & HbA_2 (HbF 1-5% , HbA_2 3.5-8% , rest is HbA)
If 3 α loci deleted (Genotype ––/– α): 3. Hemoglobin H disease (HbH) ✓ significant microcytic hypochromic anemia (Hb 6-7) ✓ Destruction of RBCs containing the abnormal HbH so → moderate to severe hemolytic anemia, splenomegaly, hypersplenism, icterus (jaundice).	3. Thalassemia intermedia ✓ Intermediate anemia (Hb 7-11) ✓ Not transfusion dependent (no regular transfusions).
If 4 α loci deleted (Genotype ––/––) : 4. Hydrops Fetalis ✓ Barts Hb (4γ) ✓ Baby is stillborn (dead when born)	4. Thalassemia major. (homozygous) ✓ Severe anemia (Hb less than 5) ✓ Features: • Hepatosplenomegaly • Expansion of bone marrow space → bones distortion • Skeletal abnormalities (in poorly transfused) • Growth retardation, delayed puberty • Other: endocrine (diabetes mellitus, hypothyroidism), cardiac (arrhythmias, CHF), hepatic (cirrhosis, liver failure) ✓ Transfusion dependent ✓ Hb electrophoresis shows elevated HbF & HbA_2 (HbF 20-100% , HbA_2 2-7% , HbA 0-60%)

❖ Diagnosis:

- **Hb electrophoresis**
- **Peripheral blood smear:**
  - Microcytic hypochromic
  - Aniso-poikilocytosis
  - Target cells
  - Teardrop cells



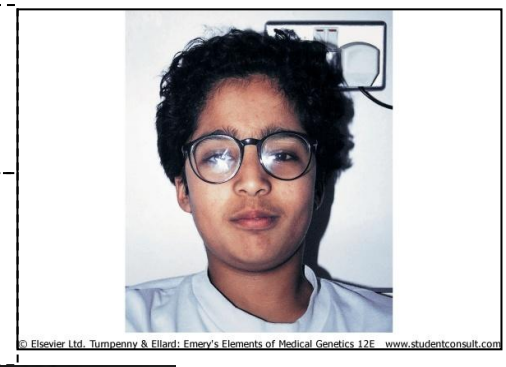


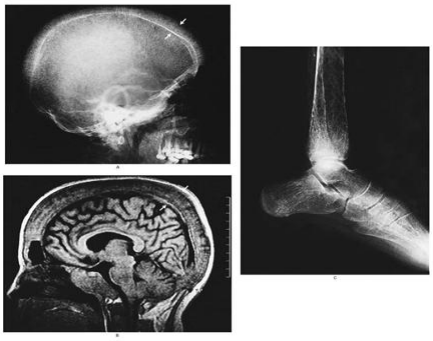


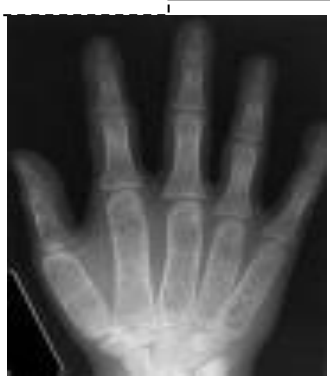
HbH inclusions in RBCs (in HbH disease)

(left image) Marrow expansion in β-thal major causing prominent cheek bones, upper jaw protrusions and skull bone expansions

(right image) Face of a child with β-thal showing prominence of the forehead (frontal bossing) through changes in skull shape as a result of bone marrow







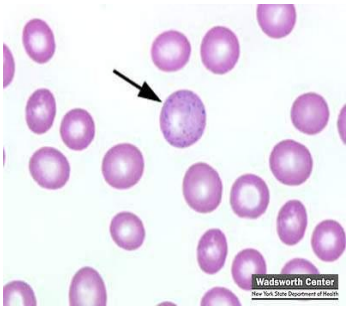
❖ **Treatment:** (thalassemia therapy for β-thal major, can also be used for HbH disease)

- ✓ Red cell **transfusion** 3-4 weekly, to maintain Hb above 9 or 10 g/dl
- ✓ Bone marrow transplant is curative in the young
- ✓ **Folic acid, 5 mg daily**
  - Splenectomy if transfusion >200 ml/Kg/yr (if splenomegaly is causing excessive transfusion needs), and **cholecystectomy for gall stones**.
  - If the patient's going to get a splenectomy, he needs to take pneumococcal and Hib (hemophilus influenza b) vaccines before the procedure, and penicillin prophylaxis after. (to avoid sepsis)
- ✓ Genetic counseling (to avoid inheritance)
- ✓ **Chelation therapy with desferrioxamine** (because they get an iron overload from multiple transfusions, and the only way to remove this excess iron is by chelation with desferrioxamine) They bind the iron and excrete it from the body. It's injectable, but now we have oral which is equally effective

c) Sideroblastic anemia & Lead poisoning:

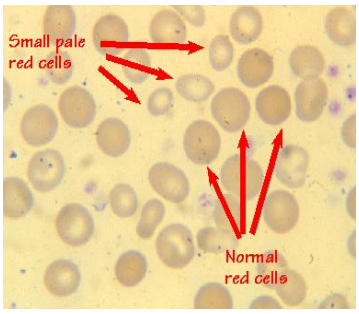
Not that important

- Lead poisoning (toxin exposure, rare cause of microcytic anemia)
- Acquired or congenital sideroblastic anemia (Caused by alcohol, lead, drugs, etc…)
  - Characteristic smear finding: **Basophilic stippling**



- Dimorphic RBCs: (not that important)

There are two populations of red cells present. One is normocytic, and the other is microcytic. This occurs either because an iron-deficient patient has been transfused or treated with iron, or in the Sideroblastic Anemias. (pale → low Hb)



(4) Normocytic Anemia

a) anemia of chronic disease:

Case example: 42 year old lady presented with anemia. She is known to have rheumatoid arthritis & diabetes mellitus on medications. She has no bleeding tendency. Examination was normal apart from mild tenderness in both the wrists. CBC showed WBC 9.6 Hb 9.3, MCV 76 fl, Platelets 433. ESR 55. Serum iron 9 (normal 12-30), iron binding capacity (TIBC) 42 (normal 52-80). Serum ferritin 115 (normal 30-300), Hb electrophoresis normal. What is the most likely cause of her anemia?

- Anemia of chronic disease **(ACD)**: RBC production can be suppressed by a chronic condition such as cancer, infection or inflammation (ex. RA, IBD, TB, SLE. Chronic renal & liver disease), which causes mild to moderate anemia. It's very common, and usually normocytic. Some cases develop abnormalities in iron metabolism, in which case there may be a microcytosis (about ⅓ of cases).

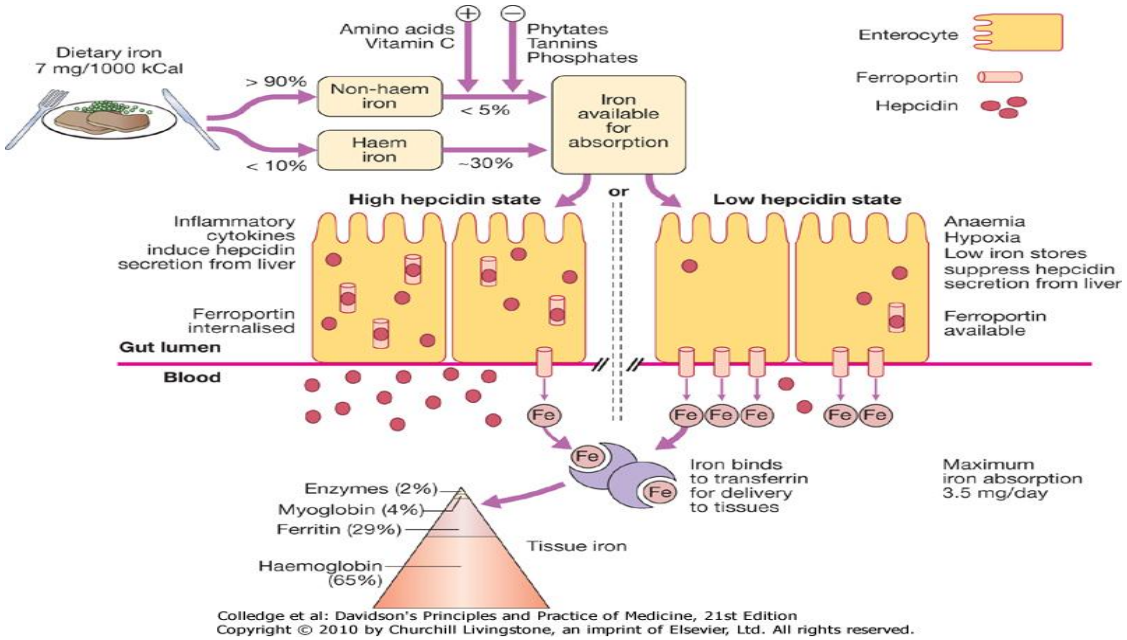
- **Pathogenesis:** How does RBC production get suppressed in ACD? By 2 main things

  1. In chronic diseases, inflammatory cells release cytokines (ex. TNF- α , IL-1, IFN-γ), these cytokines affect erythropoieses by inhibiting the growth of erythroid progenitors. So, there will be relative bone marrow (erythropoiesis) failure (suppression).
  - Serum erythropoietin levels in patients with ACD are normal when compared to healthy subjects, but much lower than levels in non-ACD anemic patients.

  2. In ACD, iron is present in the body but it's not being utilized, or in other words, it's not available for the bone marrow. The reason behind this is that the inflammatory cytokines stimulate and increase the synthesis of an acute phase protein called **Hepcidin** in the liver, which is directly involved in iron metabolism. Hepcidin inhibits iron release from cells, such as cells of the RES, which in turn reduces iron supply and further depresses erythropoiesis.

  The outcome would be: increased iron retention and storage within cells (that's why ferritin might be increased in ACD). Iron would be stuck inside cells and it's release to the blood would be decreased (that's why iron levels are low). There would also be impaired release of iron from macrophages to circulating transferrin (impaired reutilization of iron). Reduced concentration of transferrin (decreased production, increased sequestration in the spleen and in the foci of inflammation, increase loss). (that's why TIBC is low)

  3. Shortened Red cell lifespan, moderately 20-30% (from 120 to 60-90 days).



- **Symptoms:** Symptoms of the underlying disease + symptoms of the anemia

❖ **Diagnosis:**

Serum iron	Serum ferritin	TIBC	Transferrin saturation (TS)	Serum transferrin receptor
↓	↑ or normal	↓	↓	??????

Low levels of serum iron is necessary for the diagnosis of ACD

❖ **Treatment:** (treat the cause to treat the anemia)

- Treatment of the underlying disorder
- Iron supplementation (IS):
  - Benefits patients with ACD associated with autoimmune or rheumatic disorders (inflammatory conditions), and when ACD is complicated by iron deficiency (about 27% of patients).
  - However, in patients with ACD with chronic infection or malignancy, IS should be avoided. (because iron would help the infectious agent/malignant cells to grow)
- Transfusion may be required in patients who have low Hb and are symptomatic.
- Recombinant erythropoietin (measured)
- Anti-TNF-antibodies (to suppress the inflammation, although not very useful)
- Work is being done on a hepcidin antagonist (to increase erythropoiesis by increasing iron available to the bone marrow), but might be contraindicated in patients with infections or malignancy. (it's still in investigation level)

b) Hemolysis:

❖ Hemolysis is defined as the premature destruction of red blood cells, from whatever cause.

❖ **Diagnosis:** (simple tests) (note: acute hemolysis may be macrocytic)

	level	notes
Reticulocyte count	↑	as a compensatory mechanism (you'll find nucleated RBC precursors in the blood)
Indirect bilirubin	↑	(unconjugated). due to degradation of heme, because RBCs are destroyed
Serum LDH	↑	released when RBCs are destroyed (lactate dehydrogenase indicates tissue damage)
Serum haptoglobin	↓	Free hemoglobin is toxic to cells and binding proteins have evolved to minimize this risk. Haptoglobin is an alpha2-globulin produced by the liver which binds free hemoglobin, resulting in a fall in levels of free haptoglobin (because they're all bound).

- Once we've established a diagnosis of hemolytic anemia through the previous tests, we should find out what the underlying cause is.

❖ **Causes:**

- Inherited abnormalities, in:
  - The RBC membrane (Hereditary spherocytosis)
  - Hemoglobin (Sickle cell anemia)
  - Enzymes (Glucose-6-phosphate dehydrogenase (G6PD) deficiency)
- Acquired causes:
  - Immune (warm and cold autoimmune hemolytic anemia)
  - Non-immune (microangiopathic hemolytic anemia (MAHA) like TTP, HUS & DIC)
  - Could also be due to drugs

- We're going to talk about those causes, so let's start by the most important one.

1- Sickle cell anemia

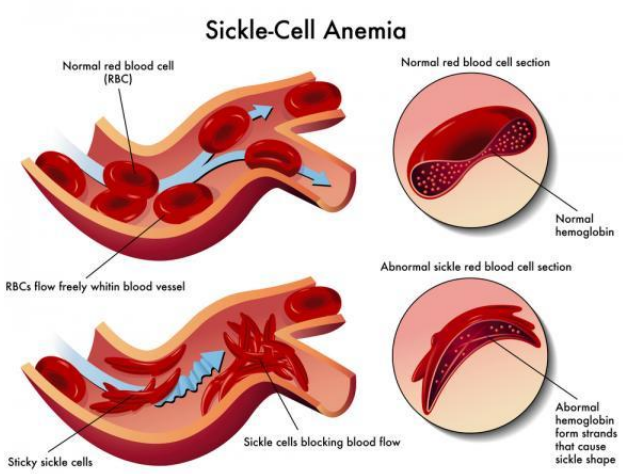
- ❖ It is an autosomal recessive disorder that results when the normal HbA is replaced by the mutant HbS
  - This happens by replacement of valine by glutamic acid at position 6 of the beta globin polypeptide chain.

- ❖ **Genotypes:**

SS (homozygotes)	sickle cell anemia /disease	produce only abnormal beta chains that make HbS
SA (heterozygotes)	sickle cell trait – asymptomatic	produce a mixture of normal & abnormal beta chains that make HbA & HbS
SC	HbSC disease	HbS + HbC
S-thal	sickle cell + beta thalassemia	

- ❖ **Pathogenesis:**
  - In sickle cell patients, under reduced oxygen conditions (ex. acidosis, hypoxia, changes in temperature, dehydration, and infection) the Hb molecules polymerize, causing the RBCs to sickle. Sickled RBCs obstruct small vessels, leading to ischemia. This results in acute syndromes termed "crises", and chronic organ damage. (with deoxygenation, HbS crystallises & gels)

- ❖ **Diagnosis:**
  - Anemia findings
  - Peripheral blood smear: shows sickle shaped RBCs (crescent shaped)
  - Hb electrophoresis

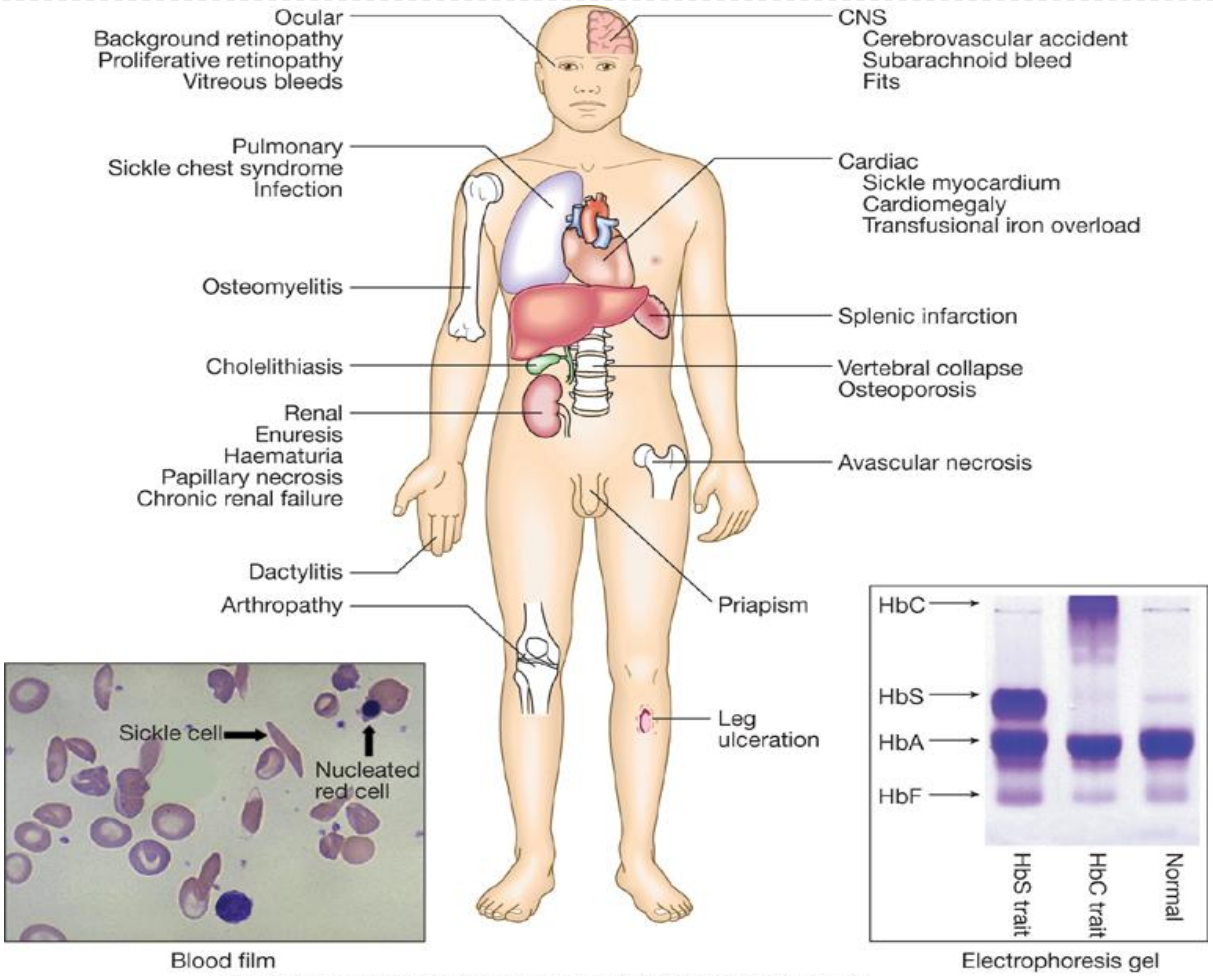


- ❖ **Clinical features:**
  - It's a chronic, compensated anemia. Onset at 3-4 months old.
  - ➢ Vaso-occlusive (painful) crisis: The most common crisis. Plugging of small vessels in the bone produces acute severe bone pain. This affects areas of active marrow: the hands and feet in children (so-called **dactylitis**) or the femora, humeri and vertebrae in adults. Muscles, lungs and intestines are also affected. (**recurrent painful episodes**)
  - ➢ acute chest syndrome: The most common cause of death in adult sickle disease. Bone marrow infarction results in fat emboli to the lungs which cause further sickling and infarction (& infection).
  - ➢ Sequestration crisis: Thrombosis of the venous outflow from an organ causes loss of function and acute painful enlargement. In children the spleen is the most common site. Recurrent sickling in the spleen in childhood results in infarction and **adults may have no functional spleen (splenic atrophy)**. Capsular stretching in adults liver may happen.
  - ➢ Aplastic crisis: Infection of adult sicklers with human parvovirus B19 (erythrovirus) results in a severe but self-limiting red cell aplasia.
  - ➢ Hemolytic crisis

- Almost every organ can be involved in sickle cell disease: (imp. For MCQs)

Heart	**Cardiomyopathy** (CHF)
CNS	**CVA (stroke)**, meningitis
GI tract	Gall bladder disease (stones,cholecystits) from bilirubin
Bones	**Avascular necrosis (ex. of femoral head; hip pain)**, osteomyelitis
Lungs	Infections , chronic diseases (ex. pulmonary fibrosis)
Kidneys	Hematuria, nephropathy
Eyes	Retinopathy, retinal infarcts (detachment)
Genitalia	**Priapism**
other	leg ulceration, Growth failure, **delayed puberty**, psychologic problems

Note: The only manifestations that patients with sickle cell trait might have are renal (ex. hematuria, isosthenuria) or gall stones.



❖ **Treatment:**

- Blood transfusion only given based on clinical condition, or Hb level (<6.0) or rapidly dropping.
- Splenic sequestration crisis, aplastic crisis, hyper hemolytic crisis: PRBC transfusion is indicated when anemia is symptomatic.
- Vaso-occlusive (painful) crisis: hydration by IVF, O_2 in hypoxia, analgesia by narcotics or NSAIDS and antibiotics if needed.
- Hydroxyurea: decreases number and severity of vaso-occlusive (painful) crisis.
- Bone marrow transplantation (successful, but not routinely performed)
- If alarming symptoms occur (such as acute chest syndrome, CVA, sustained priapism): do exchange transfusion + painful crisis treatment if needed.

2- G6PD deficiency

case example: A 20 year old male presented to his family doctor complaining of yellowish discoloration of the conjunctiva and darkness of urine, one week after taking an antibiotic for a urinary tract infection, past history is positive for a similar attack during childhood. What is the most likely diagnosis?

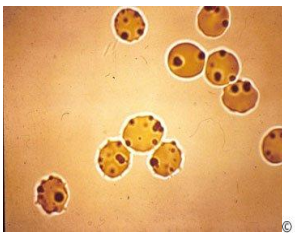
- ❖ G6PD deficiency is an X linked recessive disorder that primarily affects men.
- ❖ **Pathogenesis:** (most of the time it's silent)
  - Patients get an episode of hemolysis when they're exposed to oxidants.

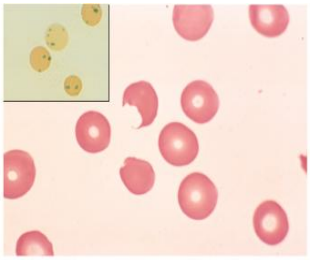
- Those oxidants are mainly: drugs (ex. sulpha containing drugs, antimalarial,…), fava beans, infection.
- They cause oxidative stress, which in G6PD deficient patients causes an episode of hemolysis.

To understand the role of G6PD, think of it as RBCs contain Hb, and Hb contains iron. And iron rusts by oxidation. But the Glucose-6-phosphate dehydrogenase (G6PD) enzyme protects the RBC from oxidative stress → thus, the iron in the Hb does not rust.

  - Severity of hemolysis depends on the enzyme variant
- ❖ **Clinical features:**
  - Jaundice (from bilirubin), dark urine (from hemoglobin)
- ❖ **Diagnosis**:
  - Peripheral blood smear shows:
    - Heinz bodies (they're like rusted iron)
    - Red cells appear blistered

    (Secondary to phagocytosis of heinz bodies by splenic macrophages)
  - G6PD screen, may be normal during hemolysis





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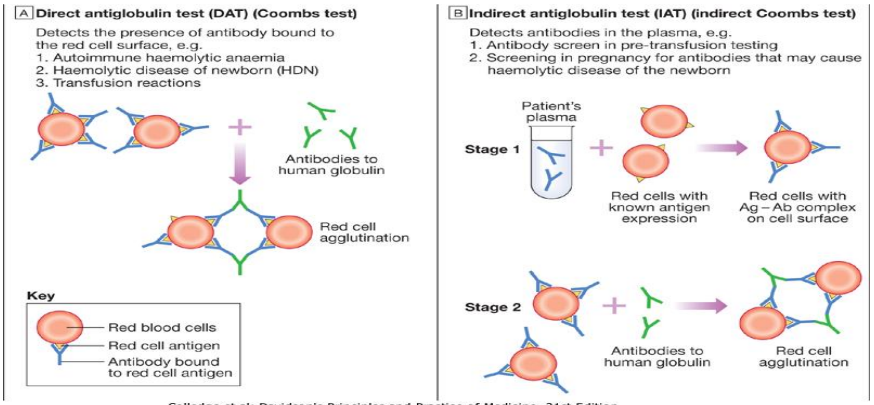
- ❖ **Treatment:**
  - Therapy: PRBC transfusion (when needed), IVF (hydration), urine alkalinisation, folate.
  - Prevention: avoid oxidants, fava beans.

3&4- Autoimmune hemolytic anemia (AIHA) & Hereditary spherocytosis

- ❖ AIHA: is a hemolytic anemia where antibodies bind to RBCs membranes → taking parts of it away → RBCs lose parts of its cytoskeleton → losing its shape into a round shape (spherocyte)
  - Note: it is divided into:
    - warm AIHA: autoantibody binds at 37°c, might be secondary to lymphoma, leukemia, SLE, drugs such as α-methyldopa, etc. (spherocytes are present in warm)
    - cold AIHA: autoantibody binds at 0°c - 5°c, might be secondary to infection such as mycoplasma pneumonia or mononucleosis. (cold agglutinin positive)
- ❖ HS: is a hemolytic anemia where there's inheritance of a defect in the gene coding for some RBC proteins → some loss in RBC membrane → round shape (spherocyte)

- ➢ Spherocytes: spherical red cells due to disproportionate membrane loss. Either inherited (HS) or acquired (AIHA). (spherocytes function as normal RBCs but they get destroyed by the spleen)
- ➢ A **Direct Coombs' test** tells you whether the red blood cells are antibody-coated, and, in the presence of hemolysis, indicates an immune-mediated process (it's **positive in autoimmune hemolytic anemia**)
  - Note that many patients with a positive Direct Coombs' test do not have hemolysis.

    (if it's positive, you might have AIHA. But if it's negative, you definitely don't have it)



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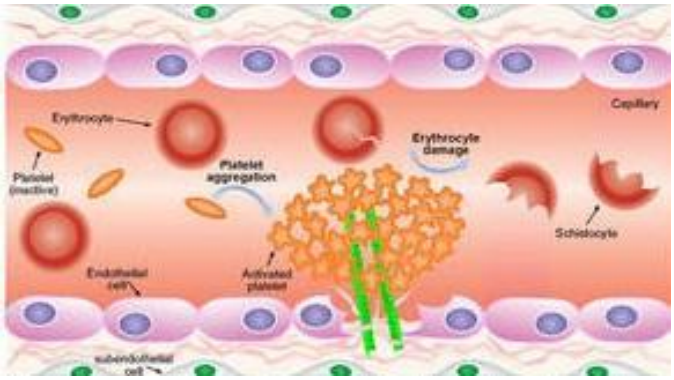
5- Microangiopathic hemolytic anemia (MAHA)

- ❖ Damage to red cells within the circulation due to platelet activation
  (blood smear shows schistocytes)

- ➢ schistocyte: a red cell which has undergone mechanical damage – synonymous with red cell fragment.



c) Aplastic anemia:

- ❖ Bone marrow failure leading to pancytopenia (anemia, neutropenia, thrombocytopenia), confirmed by bone marrow biopsy.

- ❖ Pathogenesis: T killer cell attacks cells in the bone marrow (think of it as the T killer cell suddenly wakes up not knowing who anybody is, so it starts killing them).
- ❖ Causes: different such as radiation, medications, infection… but majority is idiopathic.

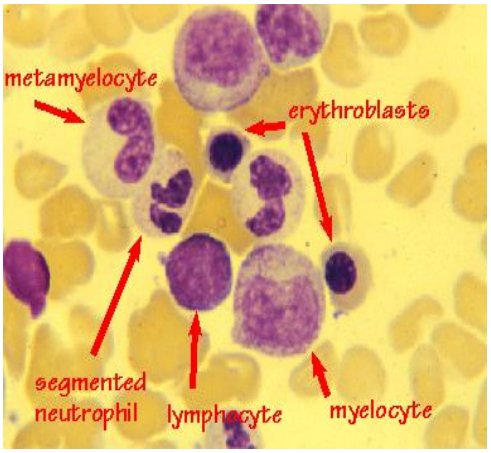
- ❖ Treatment:
- ❖ If the patient is <50 years old AND bone marrow match found → Bone marrow transplant
- ❖ If the patient is >50 years old OR no bone marrow match found → cyclosporine or antithymocyte globulins.

Erythroblasts (dr. mentioned only the underlined)

- ➢ <u>Erythroblasts are the precursor cells of erythrocytes. They contain nuclei, and in adults are only found in the bone marrow under normal circumstances.</u> Their presence in the blood may indicate either marrow 'stress', as in hypoxia, severe sepsis, or hemolysis, for example, or some fundamental bone marrow pathology such as replacement by secondary cancer.
  (If it's in the peripheral blood it's abnormal)

(3) Macrocytic anemia

Vitamin B12 & Folate deficiency (Megaloblastic anemia)



- ❖ Severe macrocytic anemia (MCV > 120 fl) → almost always indicates megaloblastic anemia

- ❖ **<u>Causes:</u>** Either reduced intake or diminished absorption.
  - Food rich in:
    - Folate include fortified cereals, cow liver, black eyed peas, etc…
    - Vitamin B12 include animal products and fortified cereal, dairy products. (so a strict vegetarian diet might cause vit B12 def.)
  - Some drugs increase folate requirements such as phenytoin.

- Vitamin B12 & Folate play major roles in cell production & DNA synthesis.
  - In cases such as hemolytic anemia, RBCs are produced in large amounts to compensate loss, this in turn consumes large amounts of folate which causes folate deficiency. So, it's useful in such cases to give folate supplementation.
- Pernicious anemia: B12 deficiency due to malabsorption.
  - It's caused by loss of parietal cells from gastric mucosa which produce intrinsic factor → leading to intrinsic factor deficiency, which is responsible for vitamin B12 absorption → leading to B12 deficiency
  - Test: - anti-intrinsic & anti-parietal cell antibodies (most specific)
    - Schilling test
  - It's also associated with degeneration of the spinal cord and gastric neoplasms

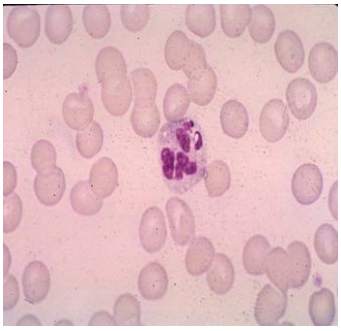
❖ **Diagnosis:**

- B12 levels / folate levels
- Peripheral blood smear:
  - Shows hypersegmented neutrophils: neutrophils with 6 or more lobes (usually means B12 or folate deficiency, but not inevitably).
    Note: neutrophils usually have 3 or 4 lobes (nuclear segments)
- A history of malabsorption might suggest B12 or folate deficiency (ex. intestinal resection → vit B12 def.)
- Note: Crohn's disease should be considered in all cases of malabsorption & megaloblastic anemias

❖ **Treatment:**

- Replace B12 or folate (depending on the deficiency)

Myelodysplastic syndrome (MDS)



- One of the common causes of macrocytic anemia in the elderly (It's a disease of the elderly).
- ❖ It's a clonal blood disorder (arising from one cell). It's a premalignant disorder where there are dysplastic features (cells in the bone marrow are dysplastic or abnormal looking)
- Most of these patients present with anemia but there's a tendency to develop acute leukemia. Most of these patients may die of bone marrow failure but about 20% may develop acute leukemia.
- Diagnosed by bone marrow biopsy
- Treatment: regular blood transfusions

Evaluation of the Patient

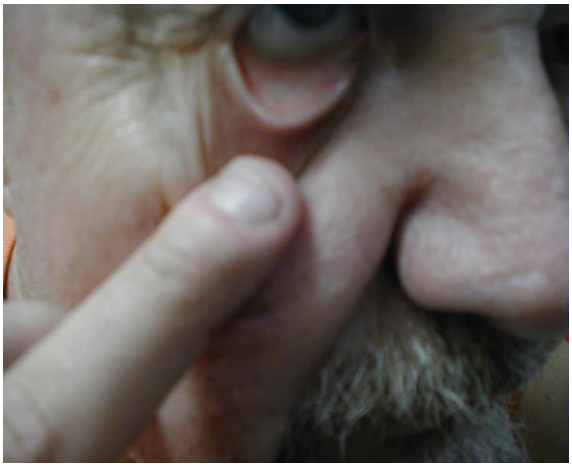
(just read through this)

■ HISTORY

- Is the patient bleeding? Bleeding from where? In females: menstrual hx, menorrhagia
  Actively? In the past? Active bleeding: patient could go into shock
- Is there evidence for increased RBC destructionn (hemolysis)? (jaundice, pallor) patient might have a liver problem, splenomegaly
- Is the bone marrow suppressed? Anemia, low platelets, infection, fever
- Is the patient nutritionally deficient? Iron deficiency anemia (escpecially in females in child bearing age 15-50, because of blood loss that is not compensated by iron)
- PMH including medication review (ex. aspirin, anrimalarial drugs), toxin exposure (ex. lead)
- Diet hx: in children not eating healthy
- Drug hx
- Anemia from childhood: mostly genetic or inherited
- Hx of painful crisis: sickle cell
- Family hx is very important

PHYSICAL EXAM

- Stable or Unstable?
  - -ABCs
  - -Vitals
- Pallor
- Jaundice
  - -hemolysis
- Lymphadenopathy (leukemia or lymphoma)
- Hepatosplenomegally
- Bony Pain (leukemia)
- Petechiae (skin bleed)
- Rectal-? Occult blood (melena, GI bleed)

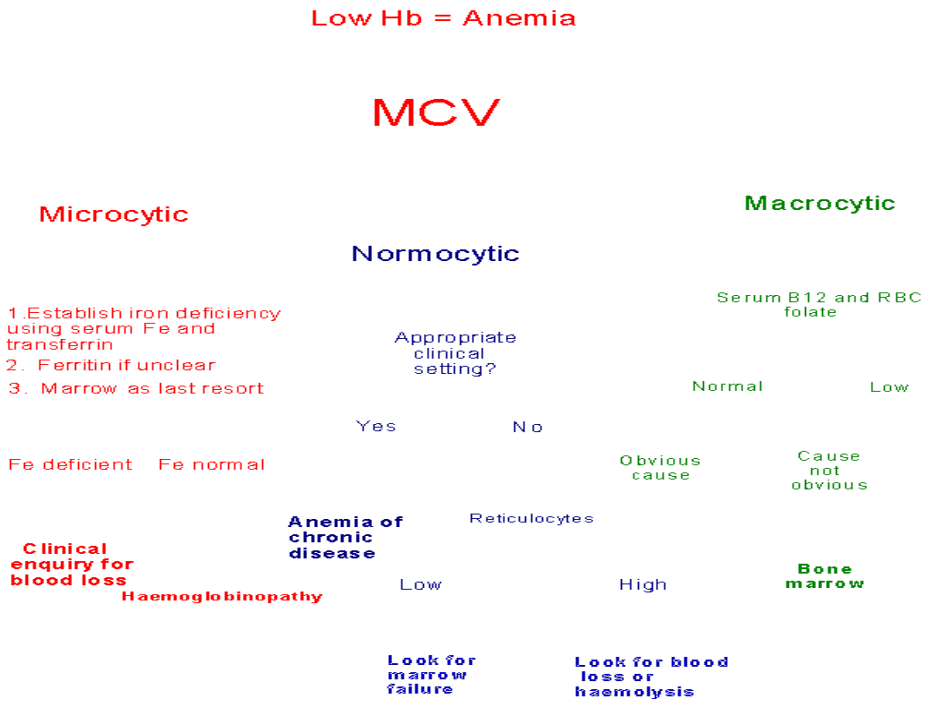


Summary

Hb conc.: in males: 13-17 g/dl, females: 12-16 g/dl

Anemia classification

(1) MCV < 80 fl. **Microcytic Hypochromic**	(2) MCV= 80 – 94 fl. **Normocytic Normochromic**	(3) MCV > 94 fl. **Macrocytic Hyperchromic**
a) Iron deficiency anemia **b) thalassemia** c) sideroblastic anemia & lead poisoning	**a) Anemia of chronic disease** (could also be microcytic) **b) hemolytic anemia** **c) aplastic anemia** d) blood loss (recent) (only Hemolytic anemia and recent blood loss have high retic. count)	**a) Megaloblastic:** • **B12 deficiency/Folate deficiency** (MCV mostly >120 fl.) **b) Non megaloblastic:** • Myelodysplastic syndrome • liver disease • alcohol • hypothyroidism cytotoxic drugs



disease	diagnosis	treatment	notes
- Iron def.	↓ iron, ferritin ↑ TIBC,RDW	Oral iron Parenteral if oral not tolerated Transfusion if severe	- Most common anemia - common in young females & preg. - Look for GI blood loss - source: red meat
Thal	Hb electrophoresis, target cells	Transfusios in major, folate, Chelate iron with desferrioxamine	- α or β , trait is asymptomatic - thal major: hepatosplenomegaly and bone distortion
- ACD	↓ iron,TIBC,TS ↑ ferritin or normal	Treat underlying disorder, Iron & transfusion sometimes, erythropoietin	- chronic conditions like cancer, infection, inflammation - hepcidin traps iron
HA	↓ haptoglobin ↑ retics,IB,LDH		- Different causes
Sickle cell	Hb electrophoresis (HbS), Blood smear	Transfusion if symptomatic, VO crisis: IVF,O2,analgesia,AB, Hydroxyurea, Alarming symp.: exchange Transf.	- SA: trait, SS: disease.. Reduced O_2: - VO crisis: painful episodes (bone) - acute chest synd.: causes death - splenic atrophy - aplastic crisis: parvovirus B19 - manifests: CVA, CHF, stones, avascular necrosis of femoral head, priapism, etc.
G6PD	blistered RBCs	Avoid oxidants	- oxidants ex.: drugs (ex.sulfa), fava beans, infection - previous episodes
AIHA	Spherocytes, +ve d.Coombs' test		
MAHA	schistocytes		
Aplastic anemia	b.marrow biopsy	<50 + match found: transplant >50 or no match: cyclosporine,ATG	
B12/F. def.	Low levels, Hypersegmented N.	replacement	- pernicious anemia: B12 def. from malabsorption. Test: anti-intrinsic & anti-parietal AB, schilling's
MDS	b.marrow biopsy	Regular transfusions	- disease of elderly, premalignant

- Read the case examples mentioned

Points from the lecture
That the doctor did not read
(If you want to read them)

- How to calculate red cell indices

$$MCV = \frac{\text{Volume of packed cells/ 1000 ml of blood}}{\text{Red blood cell count in millions/ml}} \text{ fl or } \mu m^3$$

$$MCH = \frac{\text{Hemoglobin in g/ 1000 ml of blood}}{\text{RBC count in millions/ml}} \text{ pg/cell}$$

$$MCHC = \frac{\text{Hemoglobin in g/ 100 ml of blood} \times 100}{\text{Volume of packed cells/ 100 ml of blood}} \text{ g/dl or \%}$$

← Dr. said it's nice to know but we don't use them now, because it's calculated by machines

- Polychromasia: bluish coloured red cells on film, indicating presence of increased reticulocytes.
- Myelofibrosis has tear drop shaped RBCs
- Up to 25% of hemolytic anemias will present with a normal reticulocyte count due to immune destruction of red cells precursors. Retic counts are most helpful if extremely low (<0.1%) or greater than 3% (100,000/mm^3 total).
- **<u>Blood loss:</u>**
  Acute: Traumatic, Variety of sources, Melena, hematemesis, menorrhagia
  Chronic: Occult bleeding, Colonic polyp/carcinonma
- Decreased production:
  - Nutritional Deficiency (iron, B12, Folate)
  - Neoplastic (lymphoma, myelofibrosis)
  - Anemia of Chronic Disease
  - Infectious (TB, HIV)
  - Endocrine (Hypothyroidism, erythropoietin def. in renal failure)
- Normocytic anemia also includes: bone marrow replacement, pure red cell aplasia, malignancy/marrow infiltration, transient erythroblastopenia of childhood, HIV infection, hemophagocytic syndrome.
- Cuases of folate deficiency also includes: chronic hemolysis, drugs like phenytoin and sulfa.

- **Diagnostic approach – <u>History:</u>**
  - Age : Iron def rare without blood loss before 6 months in term infants.
  - Family History & Genetics:
    (1) X-linked: G6PD deficiency
    (2) Aut dominant: Spherocytosis
    (3) Aut recessive:Sickle cell,Fanconi anemia
    (4) Family member with early age of cholecystectomy/splenectomy
    (5) Ethnicity (Thalassemia: Mediterranean; G6PD def: (Greeks, Blacks, Middle eastern)
    (6) Race:B-thal:Mediterranean,African,Asian; A-thal: Blacks, Asians
  - Nutrition: (1) Cow's milk diet: iron def.
    (2) Strict vegetarian: Vit B12 def.
    (3) Goats milk: Folate def.
    (4) Pica: Plumbism, Iron def.
    (5) Cholestasis, malabsorption
  - Drugs: (1) G6PD: oxidants (sulfa, primaquine) (2) Immune mediated hemolysis (penicillin) (3) Bone marrow suppression(chemotherapy) (4) Phenytoin increases folate requirement
  - Diarrhoea-Malabsorption of Vit B12/Fe.
    Inflammatory bowel disease and anemia of chronic disease with or without blood loss.
    Intestinal resection: Vit B12 def
  - Infection: Giardia: iron malabsorption
    Intestinal bacterial overgrowth: Vit B12 def

Fish tapeworm: Vit B12 def
EBV, CMV, Parvovirus: BMsuppression
Mycoplasma, Malaria: hemolysis
Hepatitis: aplastic anemia
Endocarditis, HIV

- **Physical findings:**
  - Skin: Hyperpigmentation, café-au-lait spots- Fanconi anemia
    Petechia & purpura-BM infiltration, autoimmune hemolysis & thrombocytopenia
    Erythematous rash-Parvovirus, EB virus
    Butterfly rash-SLE ; Vitiligo-Vit B12 def.
  - Head: Frontal bossing-Thalassemia major
    Microcephaly-Fanconi anemia
  - Mouth: Glossitis-B12 def, iron deficiency
    Angular stomatitis-Iron deficiency
    Pigmentation-Peutz Jeghers syndrome
    Telangiectasia-Osler Weber Rendu syndrome
  - Extremities: Absent thumb-Fanconi anemia
    Spoon nails-Iron deficiency
    Dystrophic nails-Dyskeratosis congenita
  - CNS-Irritable, apathy-Iron def.
    Peripheral neuropathy-lead poisoning
    Ataxia, posterior column signs-Vit B12 def
    Stroke-Sickle cell anemia
  - Short stature-Fanconi anemia, Malnutrition
- **Laboratory evaluation:**
  - Hematology: Complete Blood Count, Retic count, Peripheral smear, ESR, G6PD, Sickling(+/- inf), Hb electrophoresis, Coombs Test, Osmotic fragility test, BM aspiration
  - Biochemistry: LFT, UE, RFT, S.Ferrtin, S.Haptoglobin, Iron, VitB12, Folate, Ceruloplasmin
  - Serology:Heterophil antibody, ANA,Viral
  - Urinalysis, microscopy, culture/sensitivity
  - Stool exam. for ova, parasites, occult blood
  - Endoscopy: upper and lower bowel
  - Imaging: US Abdomen, Skeletal radiographs, Tc pertechnetate scan for Meckels diverticulum
  - Tissue biopsy: skin, lymph node, liver
- Absence of microcytosis in both parents excludes B-thal or sickle/B-thal but not A-thal.
- In iron deficiency anemia: Between 20%-60% of pregnant women have hemoglobin levels <11 g per 100 mL. Anemia was found in 6% of white women and 17% of black women during the first trimester and in 25% of white women and 46% of black women during the third trimester.
  It is less likely to occur in women taking birth control pills and more likely to occur in women with intrauterine devices.
- Advantages of anemia of chronic disease for patients:
  - Withdrawal of iron by increased storage of the metal within the reticuloendothelial system acts to limit the availability of iron to microorganisms or tumor cells and thereby inhibit their growth and proliferation
  - Decreased hemoglobin reduces the oxygen transport capacity of the blood and decreases the overall oxygen supply, which may primarily affect rapid proliferating (malignant) tissues and micro-organisms
  - Retention and storage of iron in retucoendothelial system directly and indirectly via cytokines strongly affects cell mediated immune function
- In lead poisoning: Child has pica and is exposed to lead paint or lead dust. Removal from exposure, chelation therapy and correction of iron deficiency are important.
- Sickle cell clinical features also include:
  - Infections such as pneumococcal pneumonia, meningitis.
    Arthritis, H. influenza sepsis, salmonella & staph osteomyelitis,
    mycoplasma pneumonia, viral infections.

MCQs

1. **A high mean corpuscular volume (MCV) could be found in all of the following, except:**
   a- Anemia associated with folate deficiency.
   b- Anemia associated with beta – thalassemia minor.
   c- Anemia associated with brisk reticulocytosis.
2. **The following are true about anemia except:**
   a- There is relative decrease in the level of erythropoietin as compared to the degree of anemia in patients with anemia of chronic disease
   b- Anemia is common in patients with acute leukemia
   c- Patients with B-Thalassemia major can be treated with iron and vitamins
3. **18-year-old female presents with a history of SOB on exertion, fatigue and palpitations. She was previously well and there is no family history of blood disorders. O/E she was found to have pallor, mild tinge of jaundice, and tip of spleen palpable on abdominal exam. CBC showed: WBC 10.3 (normal differential), Hb 7.6, MCV 101 fl, and platelets 388, Reticulocytes count high 6. What is the most likely diagnosis?**
   a- hemolytic anemia
   b- iron deficiency anemia
   c- megaloblastic anemia
4. **Manifestation of sickle cell anemia include the following, except:**
   a- Prolonged painless hematuria.
   b- Aseptic necrosis of the head of femur.
   c- Immune complex nephritis.
5. **Patients with Sickle Cell Anemia commonly present to the Emergency Department with:**
   a- Bleeding episodes
   b- Painful episodes
   c- Thrombo-embolism
6. **Coomb's positive haemolytic anemia may be associated with all, except.**
   a- Delayed hemolytic transfusion reaction.
   b- Systemic lupus erythematosis.
   c- Hereditary spherocytosis.

❖ **References:**

- Lecture slides + doctor's notes
- Davidsons Principle and Practice of Medicine 21st Edition.
- Step-up to Medicine third edition
- emedicine.medscape.com
- Previous years MCQs

Answers: 1.b/2.c/3.a/4.c/5.b/6.c