HEMATOPOIETIC & LYMPHATIC SYSTEM

SUBJECT : Pathology

LEC NO. : 4

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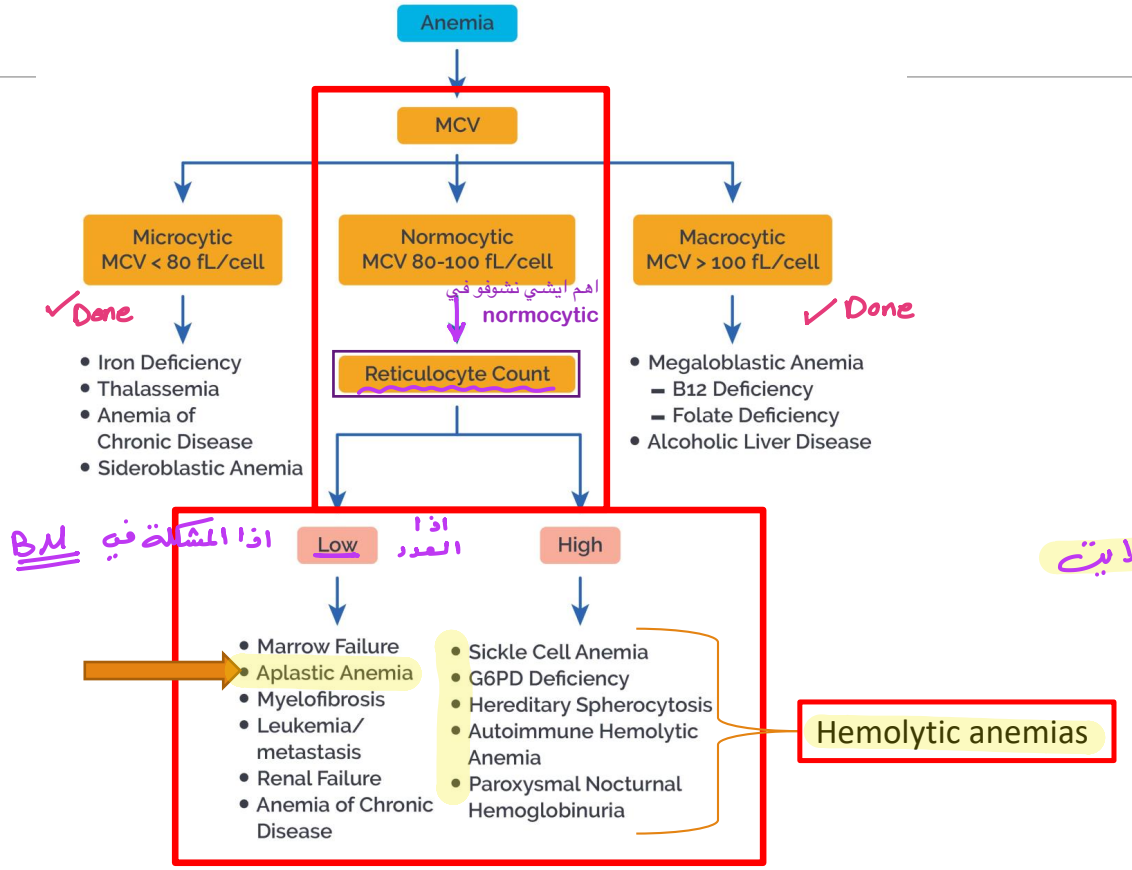
وَقُل رَّبِّ زِدْنِي عِلْمًا

CLASSIFICATION OF ANEMIAS



#إلي رح ندرس عنهم بالهايلايت

من المحاضرة ١

هاد من المحاضرة الاولى والدكتورة حكتها + حكت هاي النسب الي نعتمدها للامتحان '

Reticulocyte Index (RI)

ممكن 30 تكون وحدة انيميا

$$\text{Corrected Reticulocyte Count} = \text{Reticulocyte \%} \times \frac{\text{Actual Hct}}{\text{Normal Hct}}$$

hematocril

Normal Hct ≈ 45

$RI = 4\% \times \frac{30}{45}$

RI should be between 0.5-2.5% in healthy patients

RI < 2% with anemia = inadequate response to correct anemia

RI > 3% with anemia = compensatory production of reticulocytes

Absolute reticulocyte = blood Volume الموجودة بال R نسبة ل

→ 4% → اعلى من 3% بال انيميا وعلاجها بتشتغل

بس هون اخذتها من حجم الدم ككل فلازم اخذها من حجم الhematocrit

Normocytic Anemia

Normocytic anemia is decreased RBC mass with normal-sized RBC (MCV - 80-100 µm3)

هون ال RBC قاعدة عم تتكسر و بتتكسر يا في extravascular او intravascular

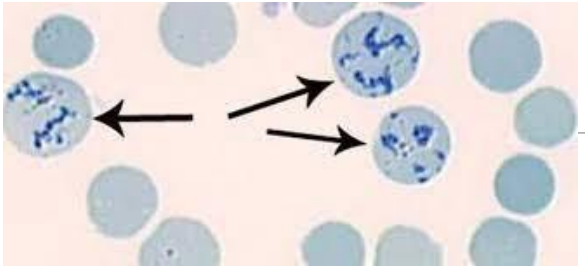
High retic count: Peripheral destruction of RBC (will have reticulocyte >3%)

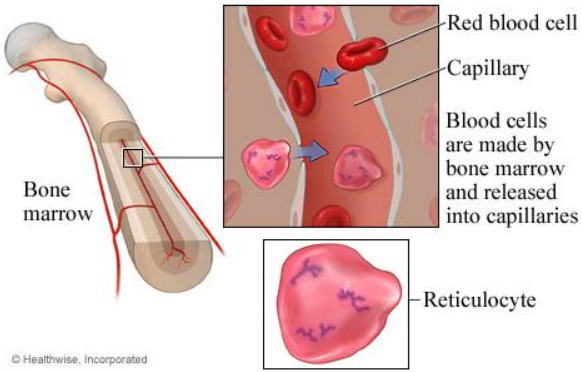
- Extravascular hemolysis (RBC destroyed by liver, spleen (mainly) and lymph) — By macrophages —> Reticuloendothelial system
- Intravascular hemolysis (RBC destroyed within blood vessels)

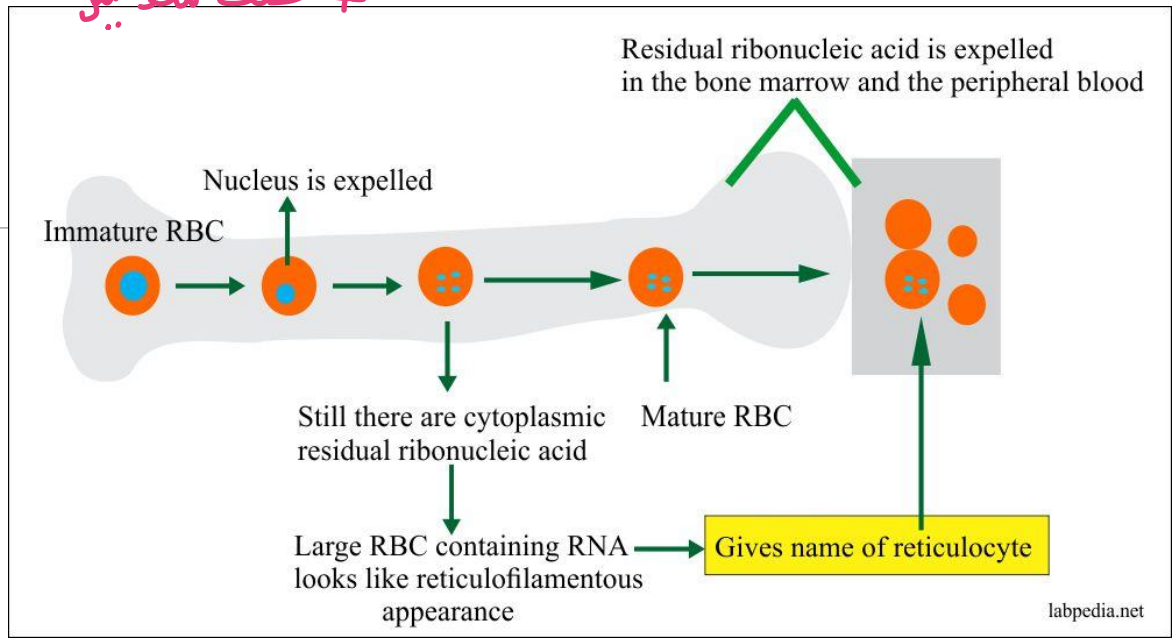
Low retic count: → المشكلة في BM *

Underproduction of RBC (no increased reticulocytes)

حكلت التذكير *



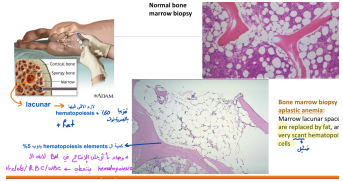




Reticulocytes

نتذكر انها المرحلة ما قبل RBC

ارجعولها ← السلايد تحت



Aplastic anemia

***عشان اسميها Aplastic Anemia لازم ما اشوف كانسر (neoplasia) ولا اشوف fibrosis ← عدم وجودهم + وجود ال fat

- Aplastic anemia is a bone marrow disorder characterized by pancytopenia due to ineffective hematopoiesis **in the absence** of any underlying neoplasia or fibrosis !!!erythropoiesis ننتبه مش
- Mostly sporadic but can be constitutional (congenital)
- Bimodal age distribution: first peak at 10 - 25 years; second peak at > 60 years

أسبابو

Aplastic anemia; etiology

Acquired aplastic anemia (most common)

- Infectious agents: parvovirus B19, HIV, EBV, Hepatitis C virus
- Toxins such as benzene ممكن لعلاج كا نسر
- Drugs, chemicals, or radiations (example of drugs: chloramphenicol)
- Autoimmune disease - most common SLE
- Idiopathic → ما فيي سبب

Constitutional "congenital" aplastic anemia; example "Fanconi anemia" بنولد فيه الطفل عندو مشكلة بعمل Aplastic anemia

Aplastic anemia; morphology

اذا اجاني مريض عملتلو cbc ولقيت pancytopenia
وعملتلو RETIC وطلع low عشان أتأكد مافي ايشي ثاني قبل ما
اخذ خزعة من ال BM

I will exclude another disease من etiology
that I know
زي vit B12 والفولك والiron
لانو نقص ال B12 و الfolic ممكن يعمل pancytopenia
اذا كان sever

لانو عندي ineffective hematopoiesis كل ال
hematopoiesis eliminates ضاربة عندي

مشو بشوف
في →

- CBC: shows pancytopenia (including normochromic normocytic anemia)
- Low reticulocyte count (< 30 x 10^9/L) → BM بسبب انو المشكلة في
- Normal vitamin B12, folate and iron (to exclude vitamin deficiency anemias)

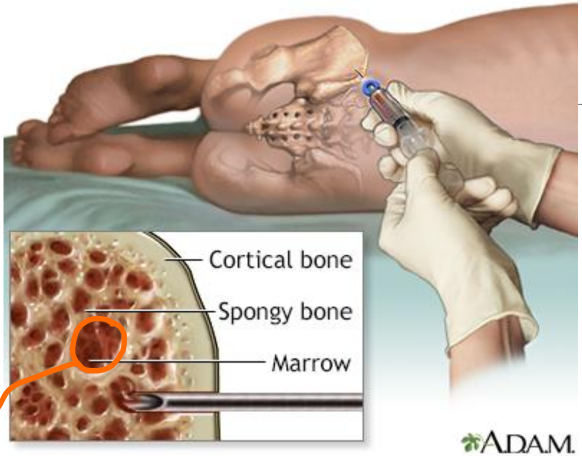
بس طلعو نوعها ل بعمل

*نقص الحديد نادر يعمل pancytopenia
*طب ليه بعمل هيك ؟عشان لو عندو نقص بواحد فيهم بعطيه
injections بدون ما اخذ منو خزعة

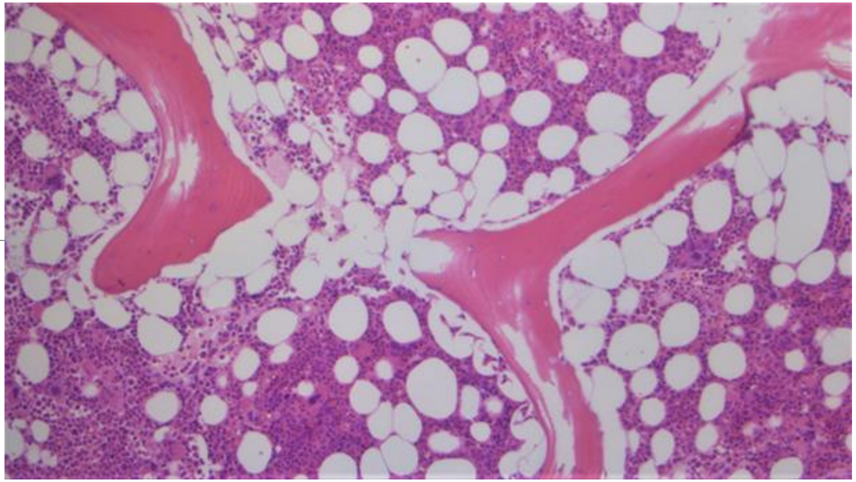
Bone marrow biopsy:

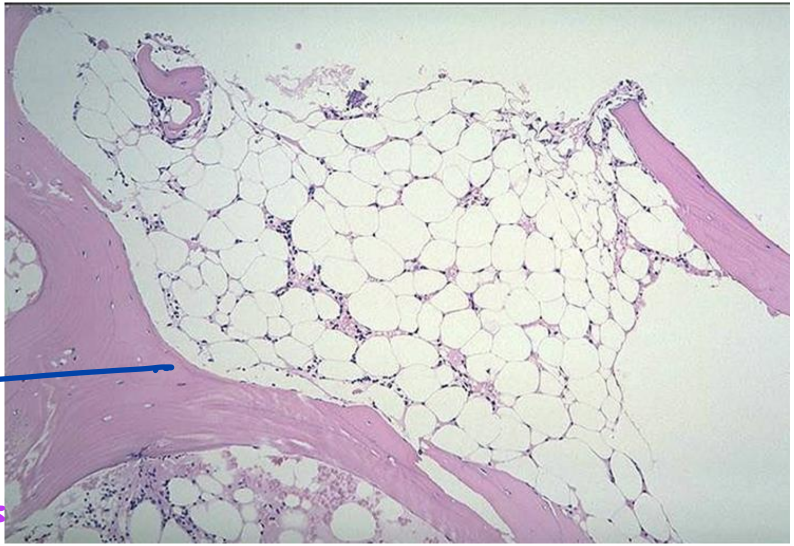
- Bone marrow markedly hypocellular (cellularity < 5%)
- Lacunar spaces replaced by fatty cells
- Residual nucleated cells include mostly lymphocytes, plasma cells, macrophages, mast cells

Normal bone marrow biopsy



lacunar → لازم الاقي فيها hematopoiesis → %60 تقريبا بالصورة فوق
+ fat





كمية ال hematopoiesis elements يدوب 5%

+ وهاد بأثر ع الإنتاج في BM لانه ال hematopoiesis بتعطي ← platelets/RBC/WBC

Bone marrow biopsy in aplastic anemia:

Marrow lacunar spaces are replaced by fat, and very scant (قليل) hematopoietic cells

ولا رح يعطيا وحدة فيهم .

Aplastic anemia; clinical features and treatment

بعتمدو على

Signs and symptoms related to severity of pancytopenia:

Anemia: most common are fatigue, shortness of breath, …..

Thrombocytopenia: bleeding and bruising

Leukopenia: frequent or prolonged infections → بسبب → ↓↓ WBC

Treatment: احطلو BM جديدة

- ✓Bone marrow transplant is the only curative treatment
- ✓Treat underlying cause if present (toxic, drugs, infections)
- ✓Immunosuppression for cases with abnormal T-cell activatio
- ✓Transfusion support only to relieve symptoms

في حالات ال Sever

عشان اخفف عن الأعراض

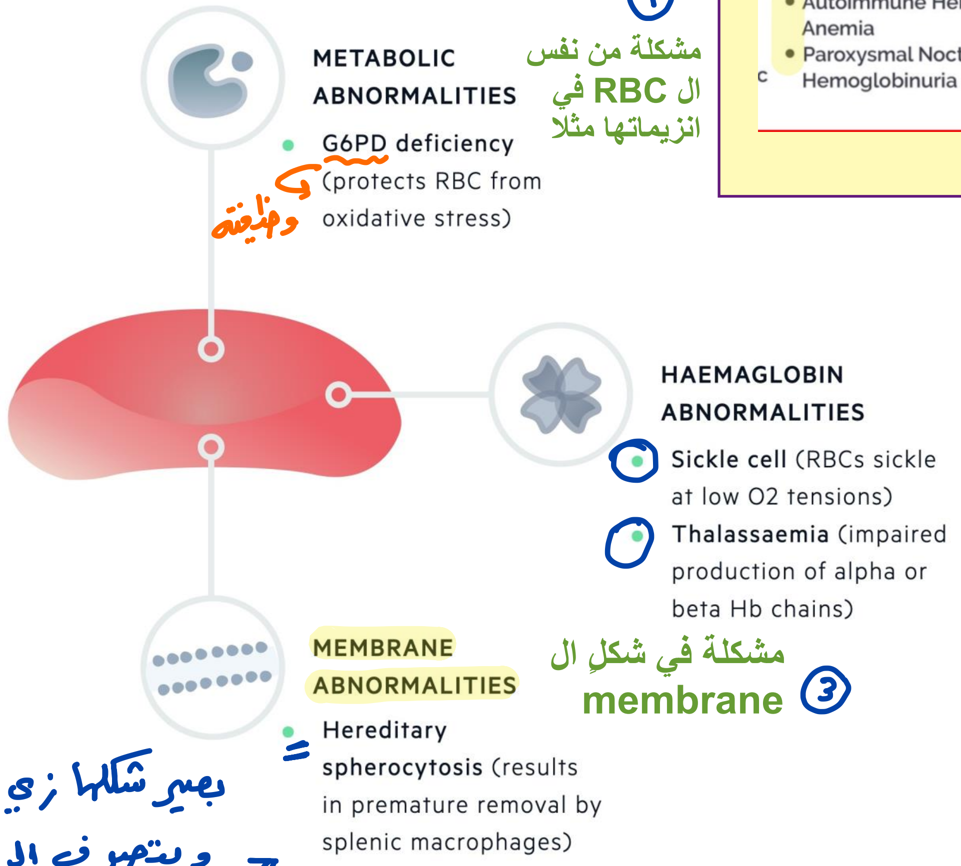
بعرف عندو مرض ما او اتسمم او باخد دوا معين … (الي انذكرو فوق)هون لازم اعالج ال infection

في بعض المرضى وجدو عندهم abnormal T cells activation وحكو انها ممكن تكون هي السبب وعم بتهاجم ال bm بتعمل replacement فحكوبنعمل immunosuppression to fat خصوصا بس يلاقو T cell activation

*شو سبب تكسر ال RBC في جسم الانسان او ليه الspleen بكسرلي اياها ؟

- Sickle Cell Anemia
- G6PD Deficiency
- Hereditary Spherocytosis
- Autoimmune Hemolytic Anemia
- Paroxysmal Nocturnal Hemoglobinuria

→ Hemolytic anemias



① مشكلة من نفس ال RBC في انزيماتها مثلا

وظيفته

② مشاكل في HB

③ مشكلة في شكلِ ال membrane

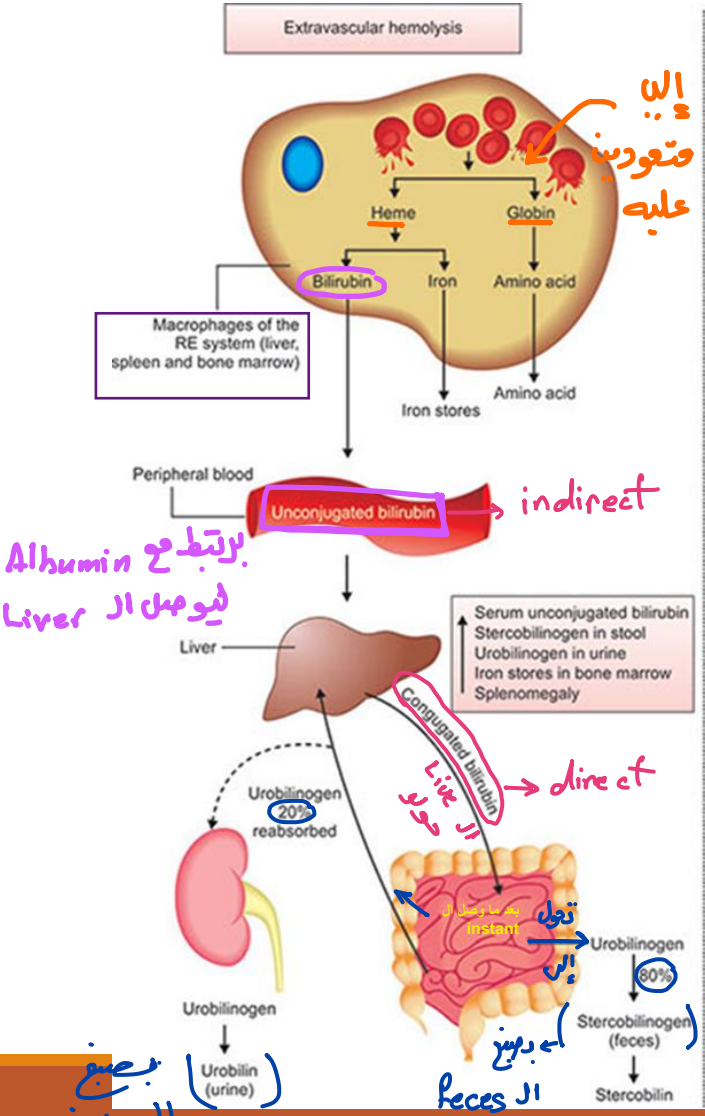
بصير شكلها زي الطابة

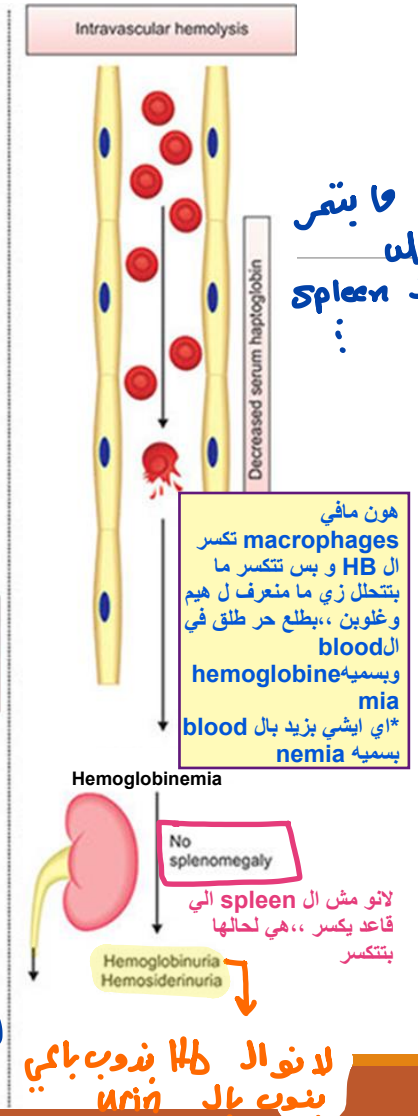
وبتشوف ال

لحد يكسرها.

Features of Hemolytic Anemia (Intra- and Extravascular)

- Shortened RBCs survival
- Elevated erythropoietin level leading to increased erythropoiesis and early release of RBCs from marrow
- Reticulocytosis
- Elevation in unconjugated Bilirubin (indirect) and LDH





Extravascular hemolysis

- Hemolysis done by reticuloendothelial system (macrophage in liver, spleen and lymph nodes)
- Globin is broken to AA; Iron is recycled
- Unconjugated (indirect) bilirubin is carried by albumin to liver and then conjugated in liver and excreted to bile.

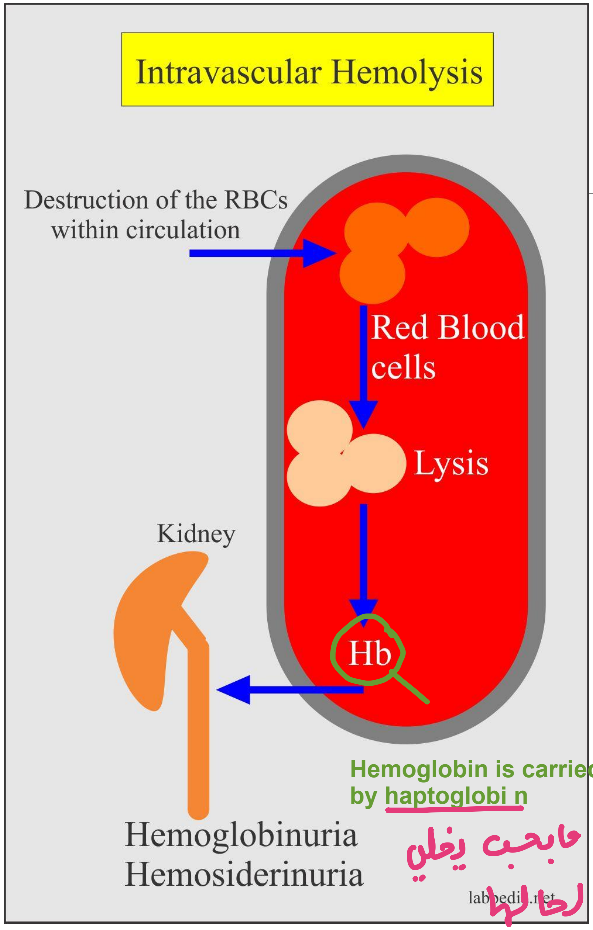
Extravascular hemolysis clinically present with:

- Anemia with splenomegaly
- Jaundice due to unconjugated bilirubin (too much bilirubin to be conjugated by liver)
- High risk for bilirubin gallstones
- Marrow hyperplasia with corrected reticulocyte >3%

لانو عم بتكسر كثير RBC وبتكون unconjugated bilirubin والكبد ما عم بلحق يعمل conjugated to all these bilirubin

↑↑ unconjugated

Intravascular hemolysis



- ✓RBC is destroyed in blood vessels. Unlike macrophage breaking down hemoglobin to bilirubin, **hemoglobin simply leaks out to blood.**
- ✓Patients will have **hemoglobinemia** and **hemoglobinuria** (hemoglobin water soluble)
- ✓Then, **hemosiderinuria** occurs after few days -→ 1 week
  Hemoglobin in urine is picked up by renal tubular cells. Iron is recycled back and stored as hemosiderin. Renal tubular cells slough off and hemosiderin will be seen in urine.

acute

Intravascular hemolysis

- Hemoglobin is carried by haptoglobin. Haptoglobin is not enough to bind all Hgb. So, patients will quickly have hemoglobinemia and hemoglobinuria

- Also, patients will show marked decrease in Haptoglobin "almost absent"

Immediate	After few days
- Decreased serum haptoglobin	- Hemosiderinuria
- Hemoglobinemia	
- Hemoglobinuria	

slough off and hemosiderin will be seen in urine.

Marrow Response To Hemolysis

- Erythroid hyperplasia with decreased Myeloid :Erythroid ratio
- In chronic cases, extramedullary hematopoiesis may take place.
- Erythropoiesis can increase up to 8 times its normal level. Thus, hemolysis may take place without development of anemia.

Anemia develops if:

- Rate of hemolysis increases beyond the compensatory rate (hemolytic crisis).
- The bone marrow stops producing RBCs (aplastic crisis)

Hemolytic anemia

هون في تداخل بينهم ما في واحد فيهم بصير totally بشكل كامل

intravascular or extravascular في واحد فيهم راح يكون predominant اكثر من الثاني

Test	Intravascular hemolysis	Extravascular hemolysis
Serum Haptoglobin	↓↓	Normal or ↓
Plasma Hb	Present	Absent
Hemoglobinuria	Present	Absent
Hemosiderinuria	Present	Absent
Serum lactate dehydrogenase LDH	↑	↑
Serum unconjugated bilirubin	Normal or ↑	↑

هي عادة بتكون نورمال بس شوية intravascular elements ترتفع شوي

عادة بتكون نورمال بس لو صار شوي extravascular elements ممكن ترتفع شوي

Intravascular

I. Microangiopathy (MAHA)

II. Acute hemolytic transfusion reaction (ABO mismatch)

III. Paroxysmal nocturnal hemoglobinuria (PNH)

IV. Paroxysmal cold hemoglobinuria (PCH)

V. Infections

VI. Snake bites/venoms

Extravascular

I. Intrinsic RBC defects
- A. Hemoglobinopathies
  - i. Sickle cell
  - ii. Thalassemias
- B. Membrane defects
  - i. Hereditary spherocytosis
  - ii. Hereditary elliptocytosis
- C. Enzyme deficiencies
  - i. G6PD deficiency
  - ii. Pyruvate kinase deficiency

II. Extracorpuscular defects مشاكل جاي من بره ما دخل RBC
- A. Immune-mediated hemolytic anemia
  - i. Autoimmune
  - ii. Drug-induced
- B. Liver disease
- C. Infections
- D. Toxins

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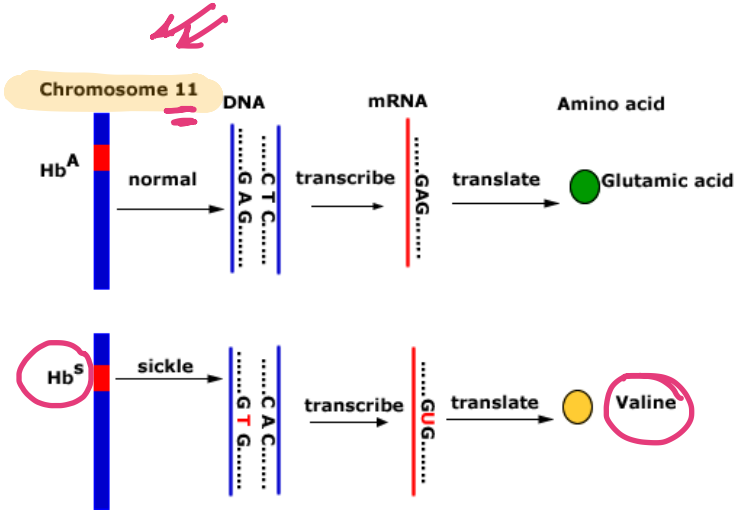
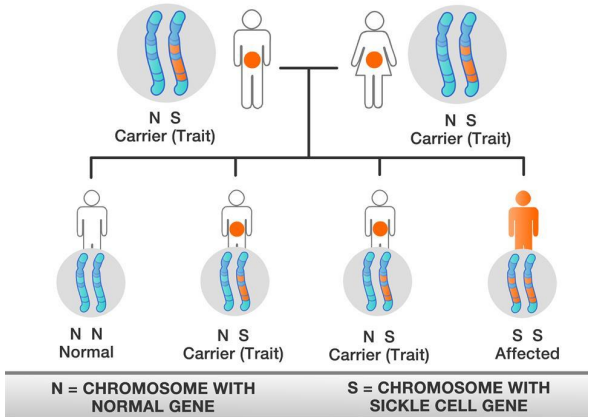




SICKLE CELL DISEASE

Is more common than thalassemia

- Most common familial hemolytic hemoglobinopathy

استبدال a.a ب a.a

- Molecular basis: single point mutation (A to T substitution) in the first exon of the β globin gene, converting glutamic acid into valine

صار ينتج HBS

Hydrophilic Hydrophobic

- It is an **autosomal recessive** inheritance

SICKLE CELL DISEASE

هون ما عندي بيتا طبيعية بالمرة

هون الأهمية:

Phenotype	Hemoglobin composition
① Sickle cell disease (homozygous mutation) — 2 Mutated	90% HbS, 8% HbF, 2%HbA_2, **no HbA** **
② Trait (one mutated and one normal B chain)	**55% HbA**, 43% HbS, 2% HbA_2

- *HbS – sickle cell hemoglobin (in $\alpha 2\beta 2$ protein, both copies of β are mutated)*

ال trait كويس هون في ما بصير لها sicklening

بس بورثها لأطفال

SICKLE CELL DISEASE

لما يجي مريض African ويكون عنده hemolysis, or anemia فكر بي Sickel cell disease

Incidence :

Especially in African

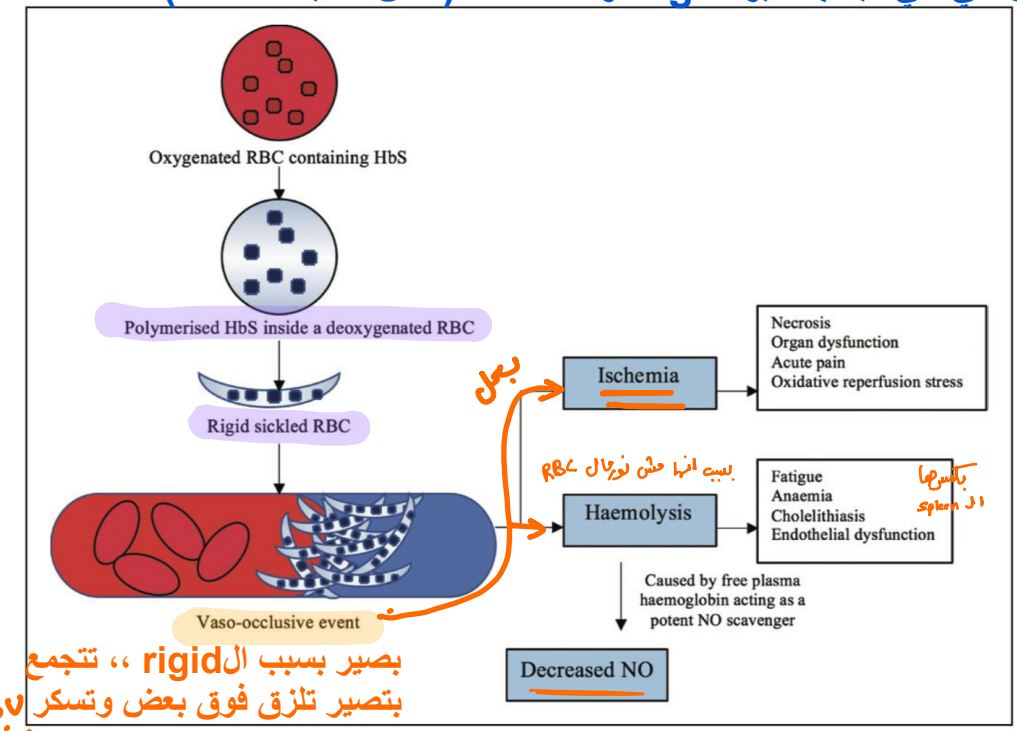
- It is more common among African & Asian population

Like thalassemia

- It was found that HbS has a protective effect against Plasmodium Falciparum malaria infection.

طب شو مشكلة HbS؟ هاد ال Hb مشكلته لما يتعرض ل hypoxia or acidosis or dehydration يصير له sickling طب ليه ؟ لانه هدول HbS بصير لها polymerization و بس يصير لها،،ال RBC بتصير Rigi sickle Rigid sickle ،، هي العملية reversible يعني على حسب المكان الي هي فيه بتصير rigid او sickle (مكان مافيه o2،...)

Pathogenesis of sickle cell anemia

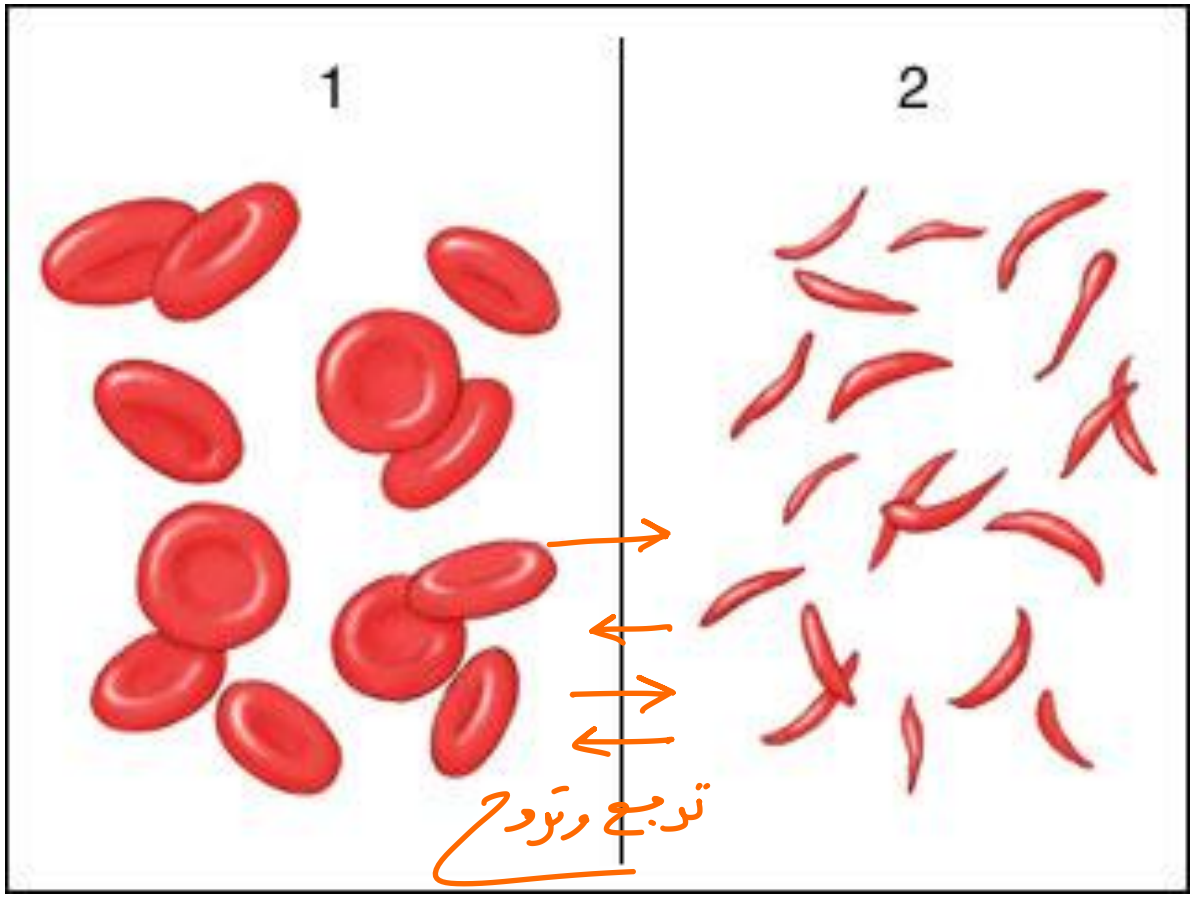


بصير بسبب الrigid ،، تتجمع بتصير تلزق فوق بعض وتسكر

- **HbS polymerizes when deoxygenated** (reversible). The polymers accumulate into needle shaped structures and make RBC sickle cell.
- Sickling increases with **hypoxemia, dehydration** and **acidosis**.
- **Note:** HbF protects against sickling. Kids protected for first few months of life.
  - ↳ like β thalassemia

Sickling and de-sickling damages membrane leading to both intravascular and extravascular hemolysis (spleen eats damaged RBC); sickled RBC cause **vaso-occlusion.**

Massive erythroid hyperplasia occur in BM to replace RBC.



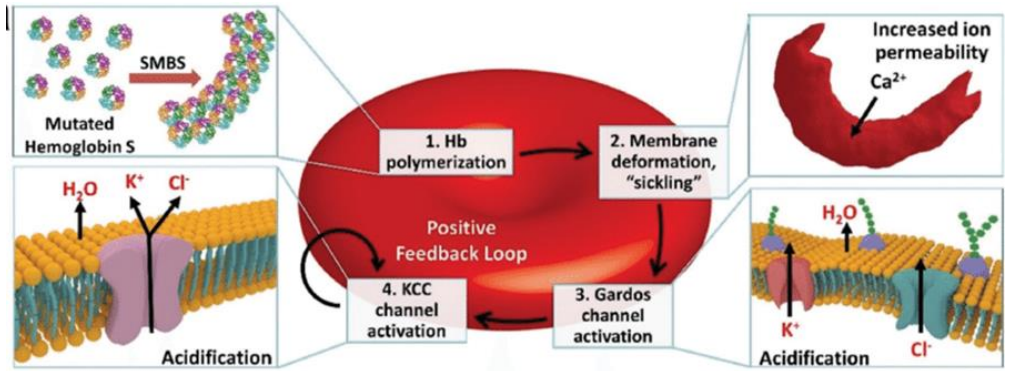
Pathogenesis of sickle cell anemia

- Sickle RBCs are rigid, less deformable and have a shortened lifespan of 10 - 20 days

- Note: repeated episodes of sickling cause cell membrane damage & then becomes irreversibly sickled, retaining their abnormal shape even when fully oxygenated

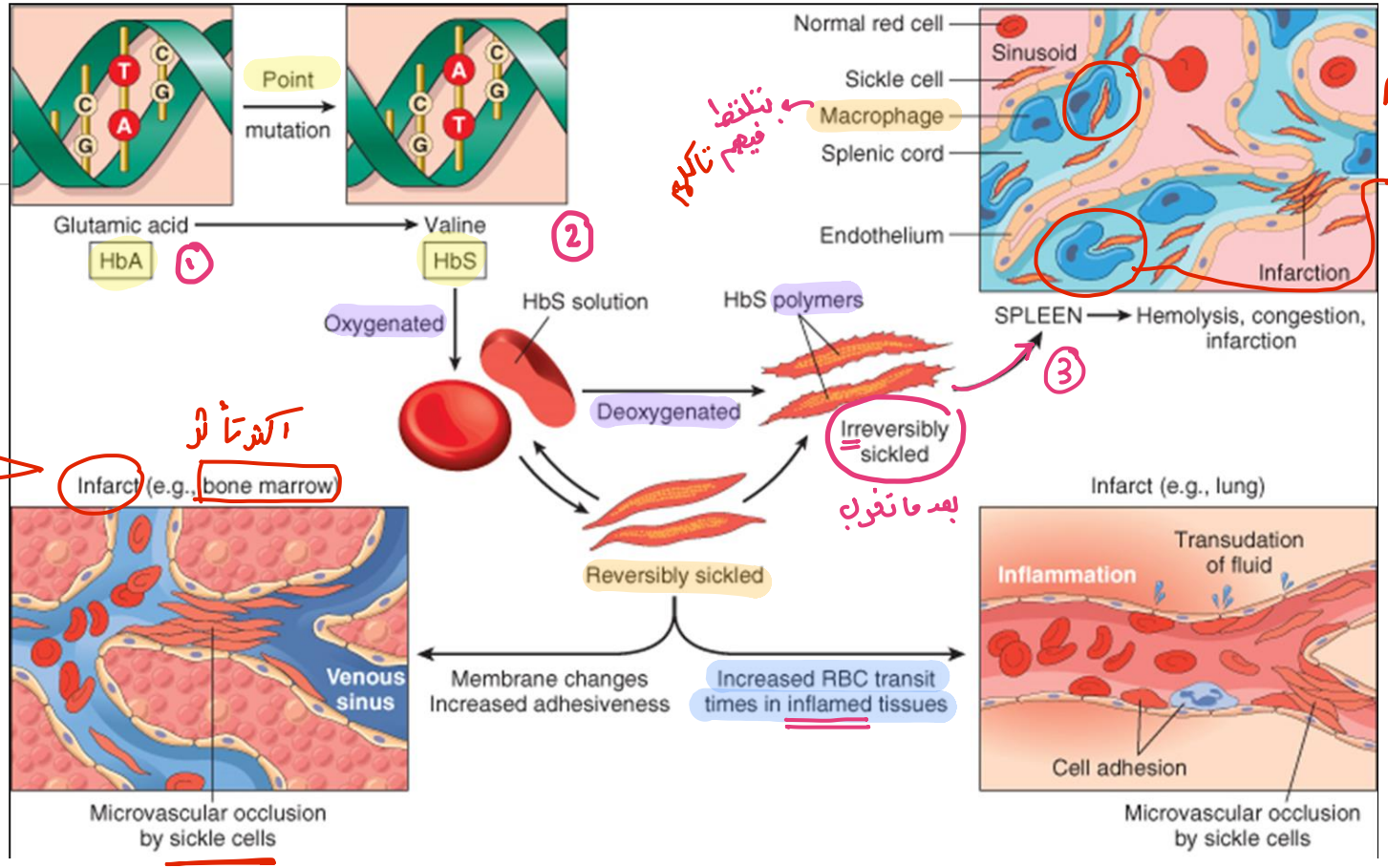
تذكر!!

- Sickling increases with **hypoxemia, dehydration** and **acidosis**.



مش مطلوبة الصورة

* تلخيص



بلزقو ببعض وبتغفر جوا ال spleen بعد فترة ممكن تفقد ال spleen بدون عملية بتلاقيه اختفى

بتلتقط فيهم تاكلهم

spleen
Kidney
:

اكثر تأثر

بعد ما تتحول

FACTORS AFFECTING THE DEFGREE OF SICKLING

ايش اللي بز يدها برضو

بدل ما نستبدل بـ Val

1. Type of Hb: Hemoglobin SC Disease ($\alpha_2\beta_2^{6\ Val}$, $\alpha_2\beta_2^{6\ Lys}$) shows a milder disease.
Also; homozygous vs. heterozygous

2. Hb. Concentration: red cell dehydration increases HbS concentration which will greatly facilitate sickling during deoxygenation and can trigger occlusion of small blood vessels .

خاصة اذا تقوشت ل ↑

Also, coexistence of α thalassemia reduces the HbS concentration; due to low MCHC

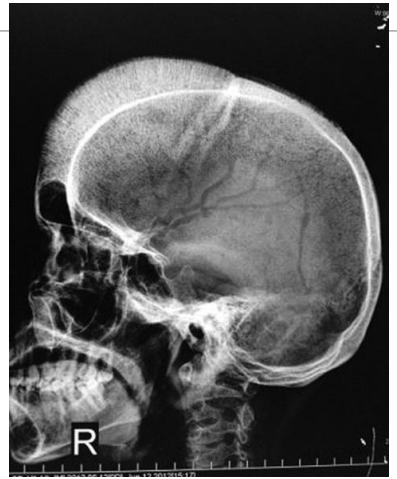
3. Blood circulation: sickling is confined to microvascular beds where blood flow is sluggish - **bone marrow , spleen & possibly kidneys.**

Also, inflammation slows the flow by increasing the adhesion of leukocytes and RBC's

HbA ← HbF الطبيعي يتحول *
HbS ← HbF بس إلي يصير ←

Sickle cell anemia; clinical consequences

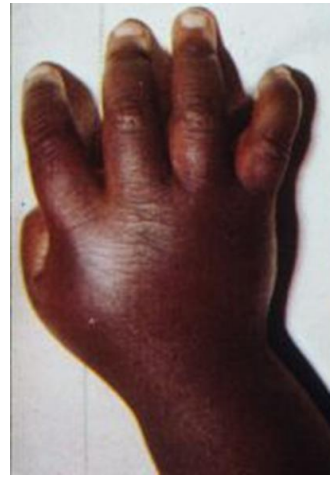
1. Chronic hemolysis: marked reticulocytosis and hyperbilirubinemia and gall stones formation. Expansion of the bone marrow due to increase erythropoiesis causes prominent cheek bones & changes in the skull. ("Hair on end" appearance on skull X-ray)



2. Ischemic manifestations (microvasculature obstruction): bones, liver, kidneys, skin, retina,…etc.

Examples

- Dactylitis is due to vasoocclusive infarcts in the bones of fingers in hands and feet, causing painful swelling
- Early common presentation in infants



2. Ischemic manifestations Examples

بختفي

- **Autosplenectomy (spleen autoinfarction),** which leads to shrunken, fibrotic and calcified spleen:

لانو ال **spleen** وظيفته يحمي الجسم من هاي ال **organelles**

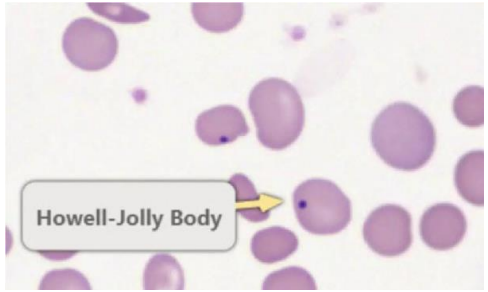
I. Increased risk of encapsulated organism infection (staph aureus, strep pneumo, haemophilus influenza)

inflammation of bone

II. Salmonella paratyphi osteomyelitis (encapsulated)

III. **Howel-Jolly bodies** on blood smear - nucleated RBC

لانو مش موجود حتى ينضف **auto splenectomy**او**splenectomy** بشوفها في حالة عمل هاي الRBC



- **Acute chest syndrome** (vaso-occlusion of pulmonary microcirculation), often precipitated by pneumonia and presents with chest pain, SOB, lung infiltrates

- **Renal papillary necrosis** – presents as gross hematuria and proteinuria

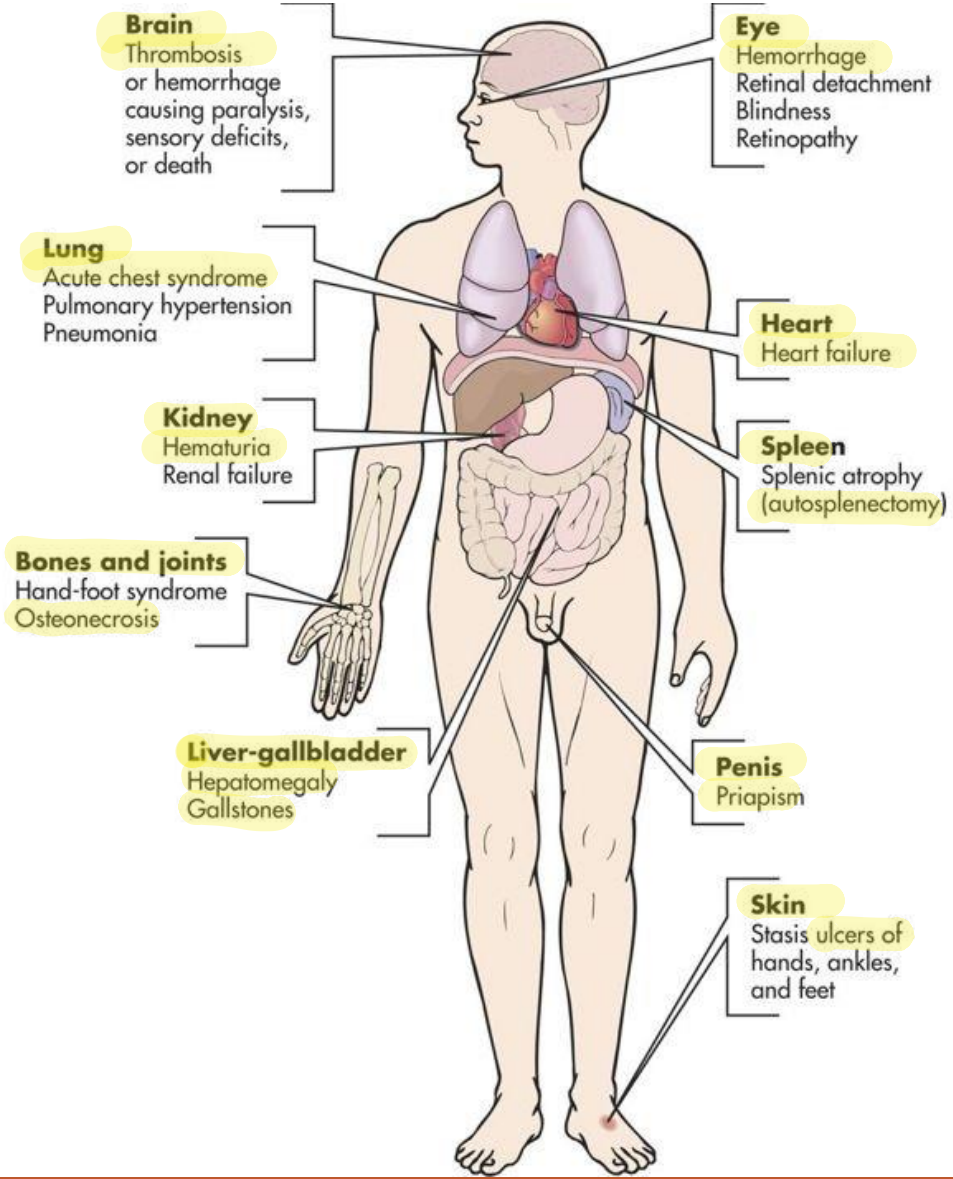
قادر اشوفه بالعين**Blood in urine**

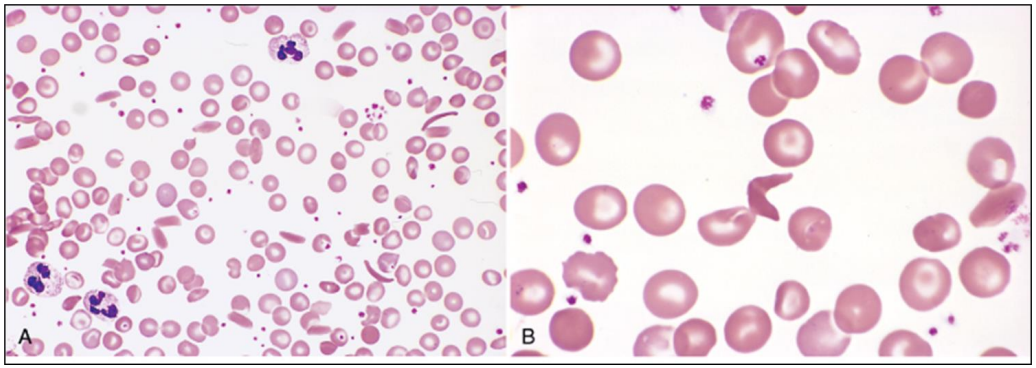
Sickle cell anemia; diagnosis and treatment

- Asymptomatic till 6 months of age. بس بيبدل HbF → HbS
- Moderate to severe anemia (6-8 g/dl).
- Unremitting course punctuated by sudden crises (pain crises, hemolytic crises).
- CBC and Hb electrophoresis (HcT is about 18% -30% - normal value 35 %-45%)

هي حكت احفظو بشكل major والي انوجد
بالسلايات فوق بس الي خططتوبالهايلايت حكتو

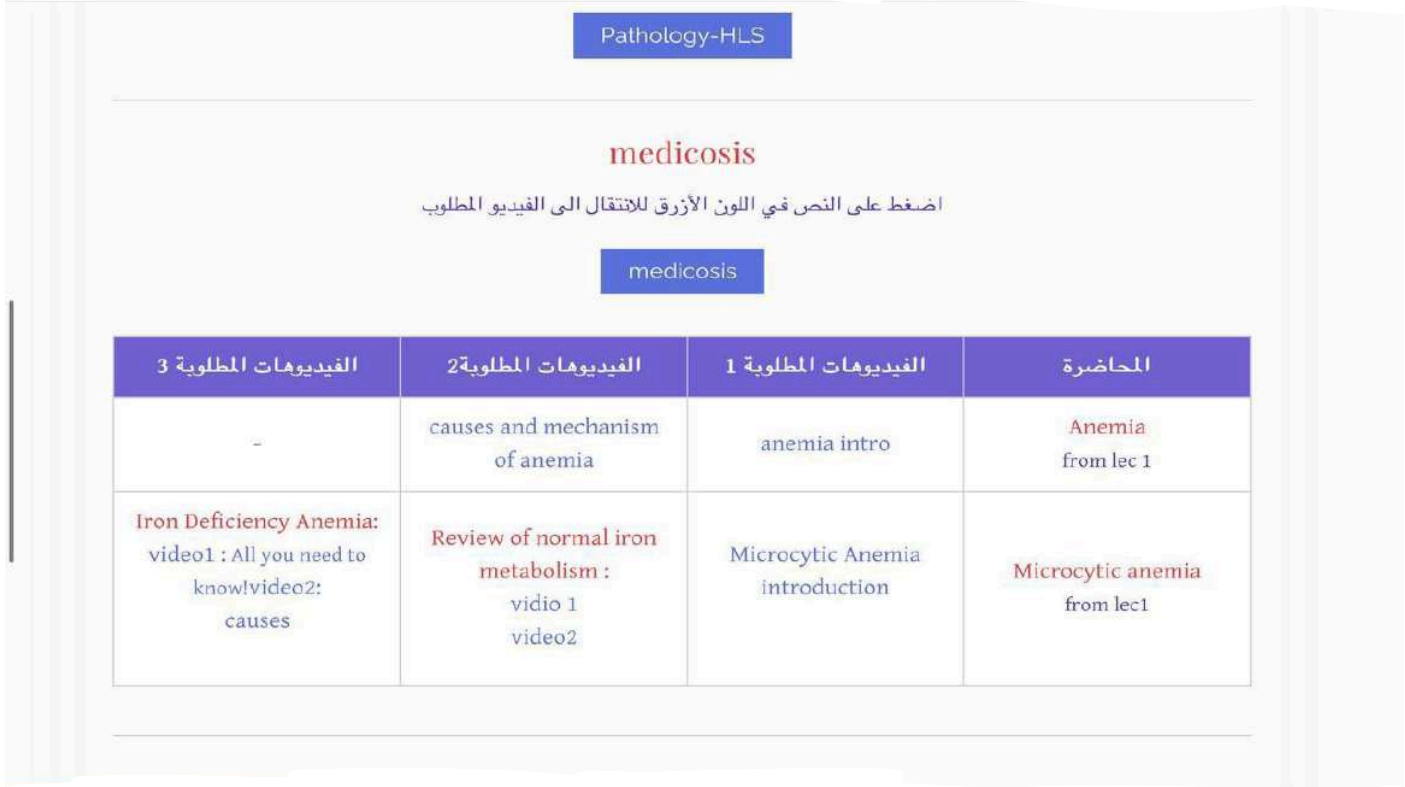
Sickle cell anemia





Treatment:

- ✓ Prophylactic treatment with penicillin to prevent pneumococcal infection .
- ✓ Adequate hydration and pain relief
- ✓ Use the hydroxyurea therapy “increase HbF”
- ✓ In severe cases, exchange transfusion to reduce the Hgb S



Pathology-HLS

medicosis

اضغط على النص في اللون الأزرق للانتقال الى الفيديو المطلوب

medicosis

المحاضرة	الفيديوهات المطلوبة 1	الفيديوهات المطلوبة2	الفيديوهات المطلوبة 3
Anemia from lec 1	anemia intro	causes and mechanism of anemia	-
Microcytic anemia from lec1	Microcytic Anemia introduction	Review of normal iron metabolism : vidio 1 video2	Iron Deficiency Anemia: video1 : All you need to know!video2: causes

وتجدون ع موقع النادي الطبي فيديوهات medicosis لمواضيع محاضراتنا
النادي الطبي من اي متصفح ، دفعة حياة ، Patho ,HLS