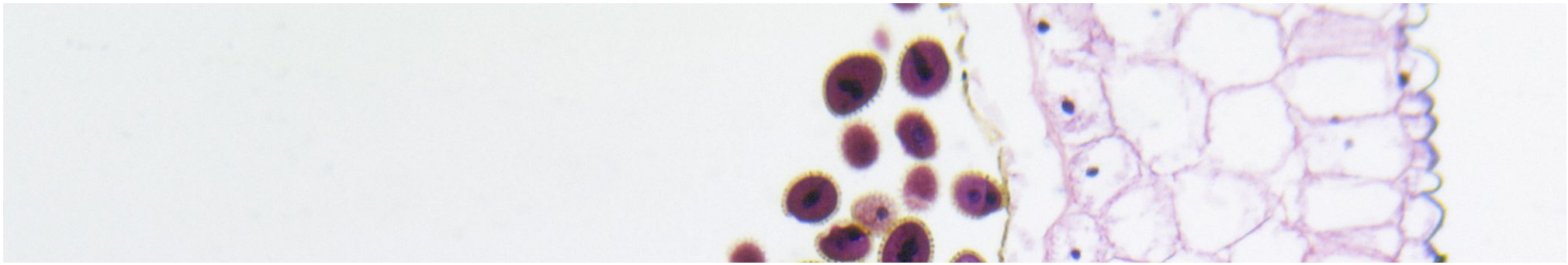

SICKLE CELL DISEASE

MOHAMMAD BIGLARI MD. MSC.

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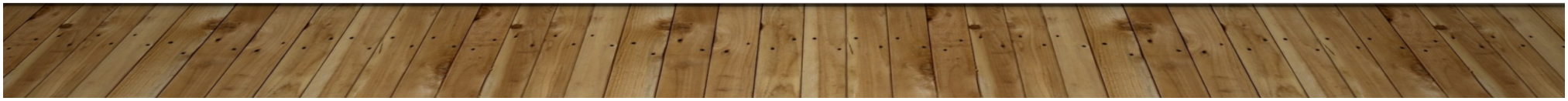
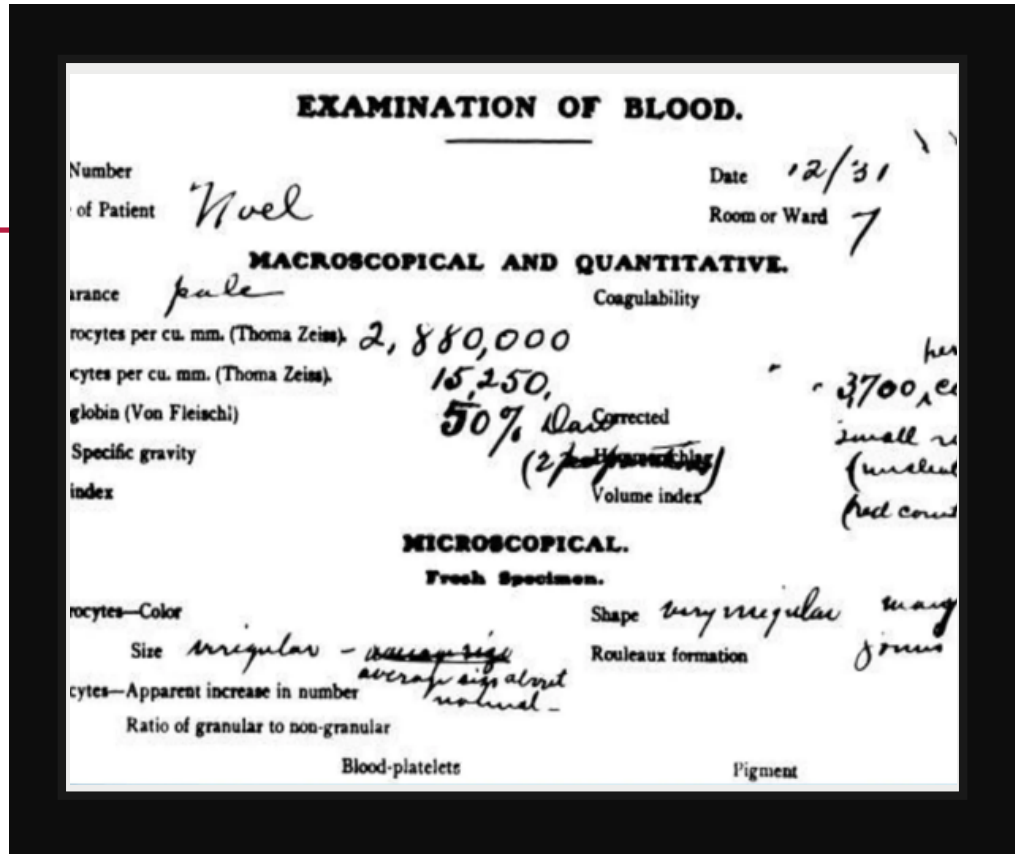
RIOHCT, SHARIATI HOSPITAL, TUMS



HISTORY

- 1904
- Walter Clemet Noel from Grenada
- Admitted with respiratory distress and leg ulcer
- Dr. Earnest Irons (intern)
- Routine blood test
- Pear shaped elongated RBCs



EXAMINATION OF BLOOD.

Number
of Patient Noel
Date 12/31
Room or Ward 7

MACROSCOPICAL AND QUANTITATIVE.

rance pale
Coagulability
rocytes per cu. mm. (Thoma Zeiss) 2,880,000
cytes per cu. mm. (Thoma Zeiss) 15,250
globin (Von Fleischl) 50% Dale Corrected
Specific gravity
index
Volume index

MICROSCOPICAL.

Fresh Specimen.

rocytes—Color
Shape very irregular many forms
Size irregular – ~~average size~~ average size about normal
Rouleaux formation
cytes—Apparent increase in number
Ratio of granular to non-granular
Blood-platelets
Pigment

HISTORY

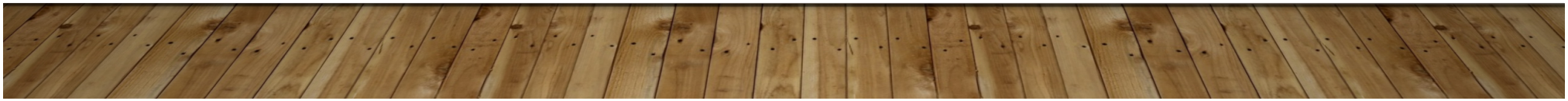
- Dr James Herrick
- The 1st documented case of sickle cell disease in 1910
- Article on peculiar elongated & sickle shaped RBCs
- Dr. Noel returned to Grenada
- He died of acute chest syndrome at 32

HISTORY

- The third case described in 1915

- A family: a symptomatic girl and asymptomatic father
- Three dead children from sever anemia

- Dr Emmel suggested the genetic basis



HISTORY

- Dr V. R. Mason
- Report the 4th case in 1922

- Named the situation “Sickle Cell Anemia”

- Notice the similarities
- Misconception of African origin

SICKLE CELL DISEASE

SCD EPIDEMIOLOGY

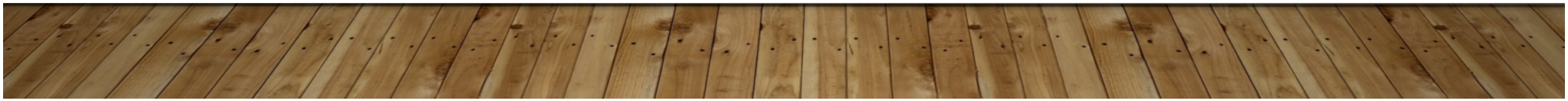
- Malaria endemic countries – Sub-Saharan Africa, Middle East, India

  - Heterozygotes are *P. falciparum* resistant

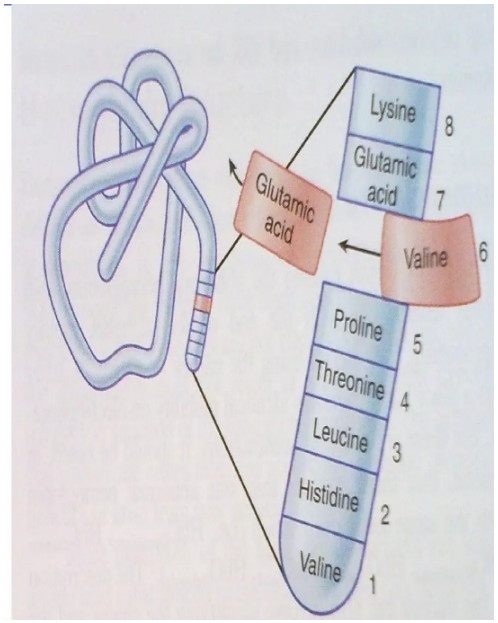
- 300,000 births annually with Hb SS (half in Nigeria)

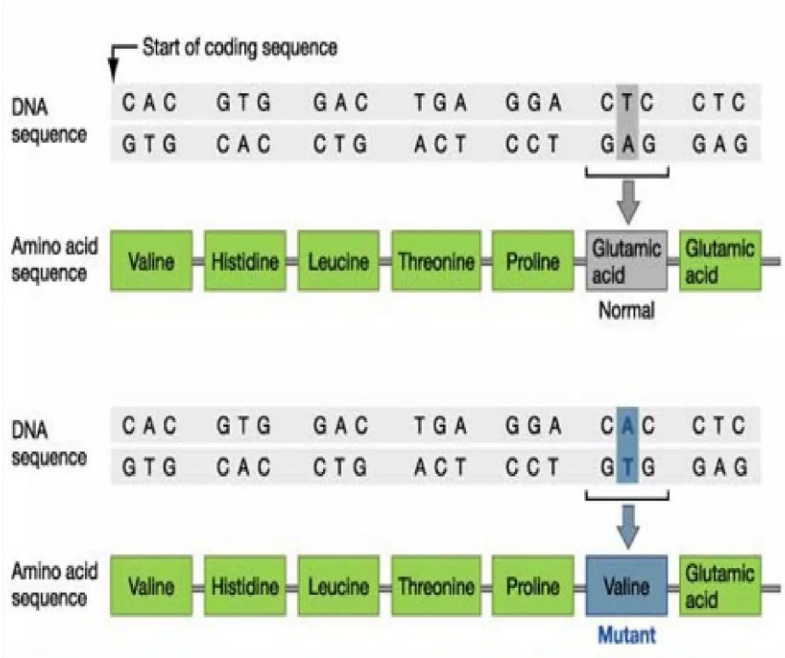
- Most of these die before age 5

- In many African countries, up to 50% of population carries Sickle Trait

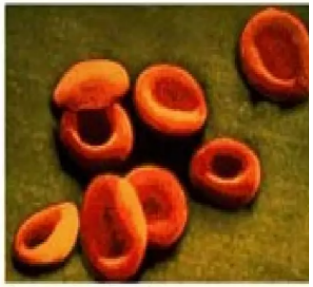


SCD ETIOLOGY



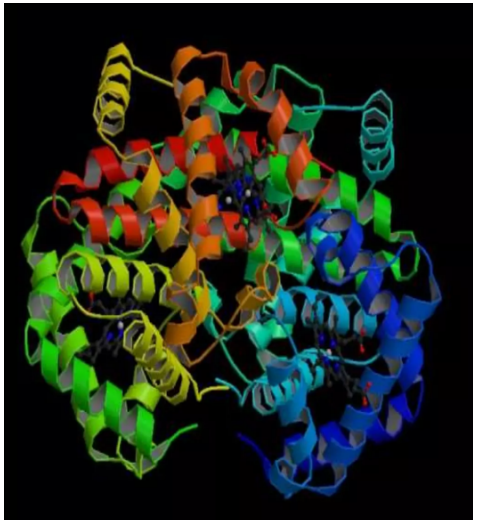


ABNORMAL Hb

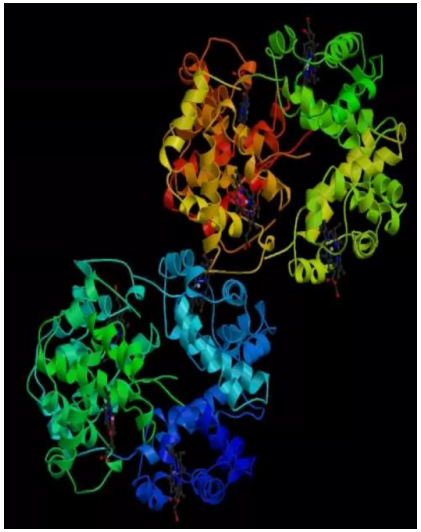


Normal red blood cells

Sickled red blood cells

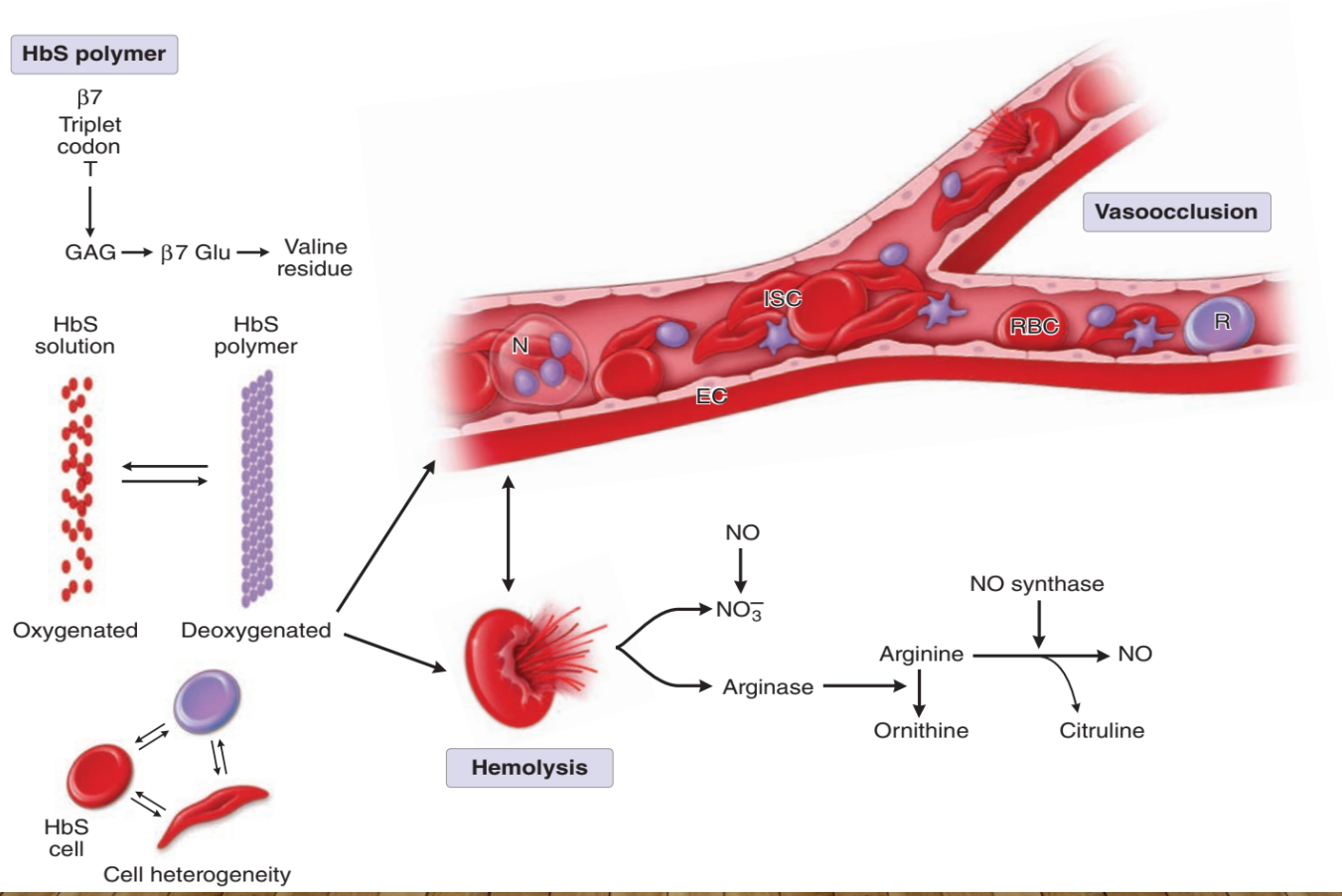


Hb A



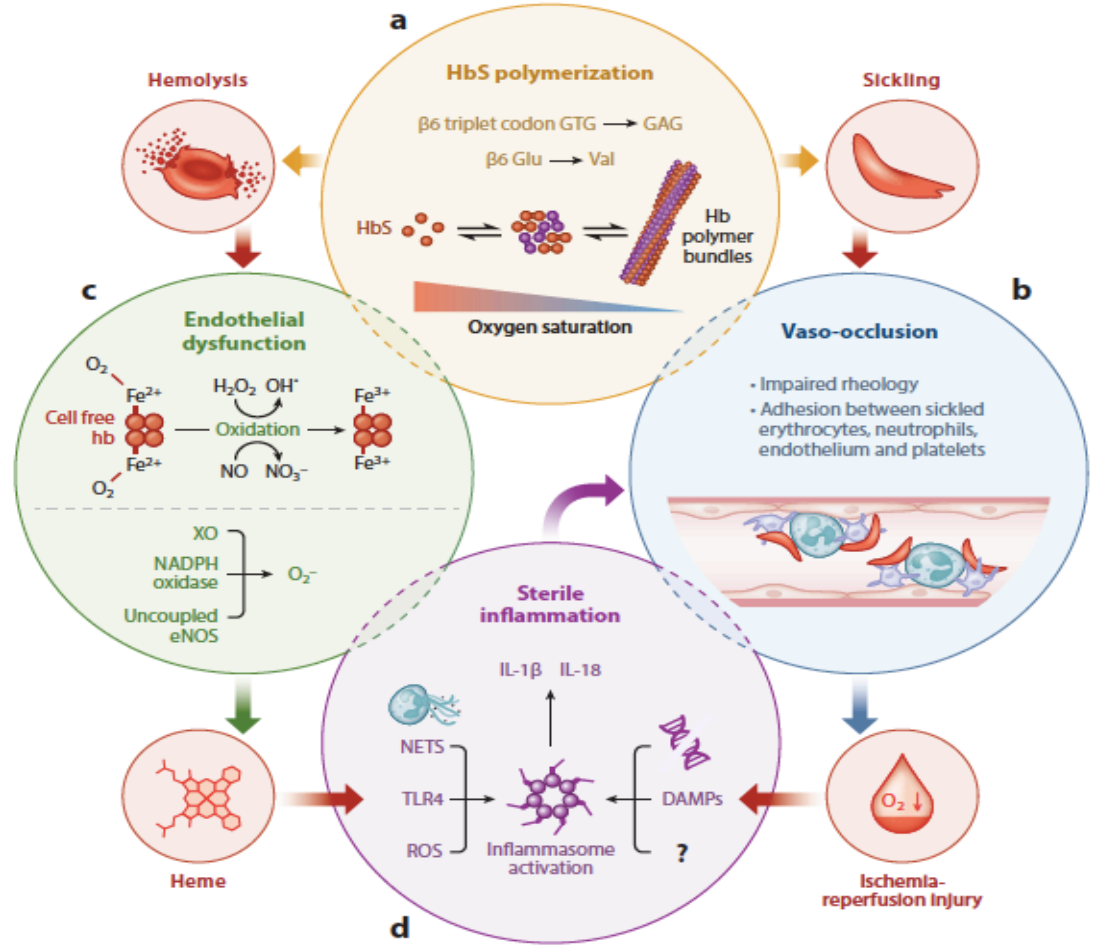
Hb S

PATHOPHYSIOLOGY OF SCD

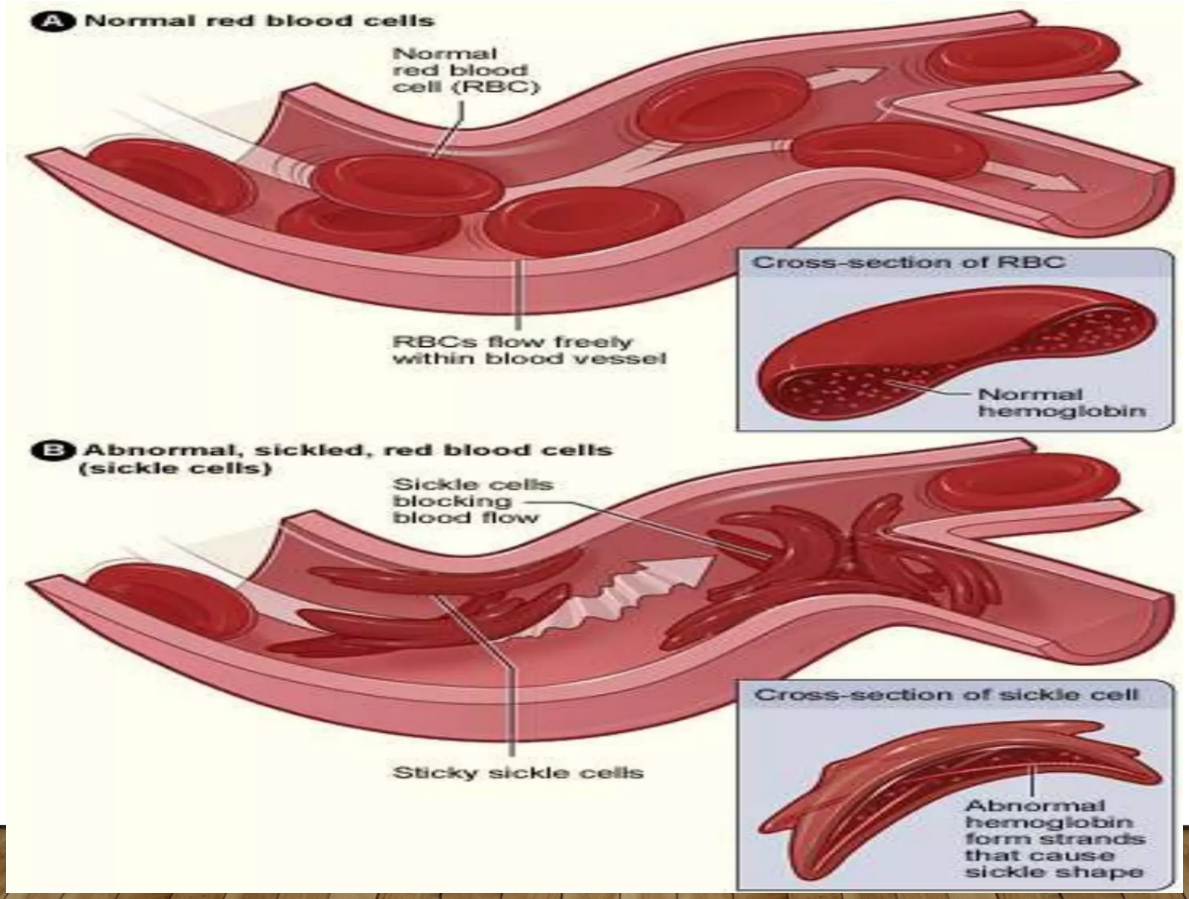


PATHOPHYSIOLOGY OF SCD

Polymerization ~ [Hb]30



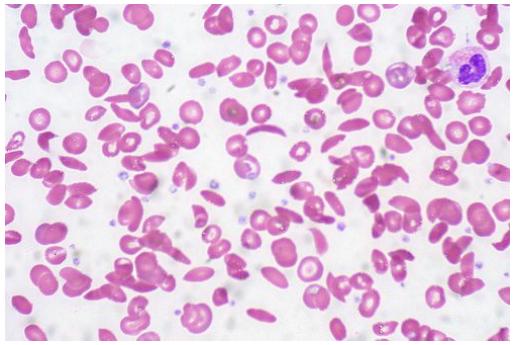
SICKLING


A Normal red blood cells
Normal red blood cell (RBC)
RBCs flow freely within blood vessel
Cross-section of RBC
Normal hemoglobin
B Abnormal, sickled, red blood cells (sickle cells)
Sickle cells blocking blood flow
Sticky sickle cells
Cross-section of sickle cell
Abnormal hemoglobin form strands that cause sickle shape

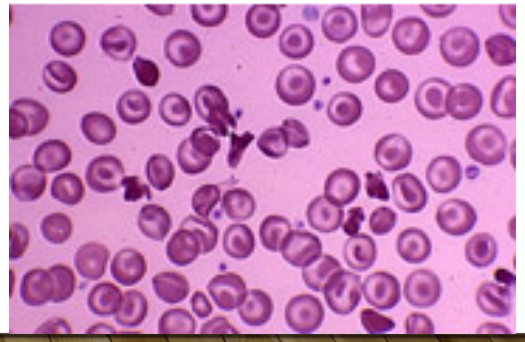
IRREVERSIBLY SICKLED CELLS (ISCS)
CLINICAL & LABORATORY CORRELATES

- Positive correlations with % of ISCs
  - MCHC
  - α-globin gene number
- Inverse correlations with % ISCs
  - RBC lifespan
  - Total Hb
  - Hb F
  - α-thalassemia
  - Frequency of pain

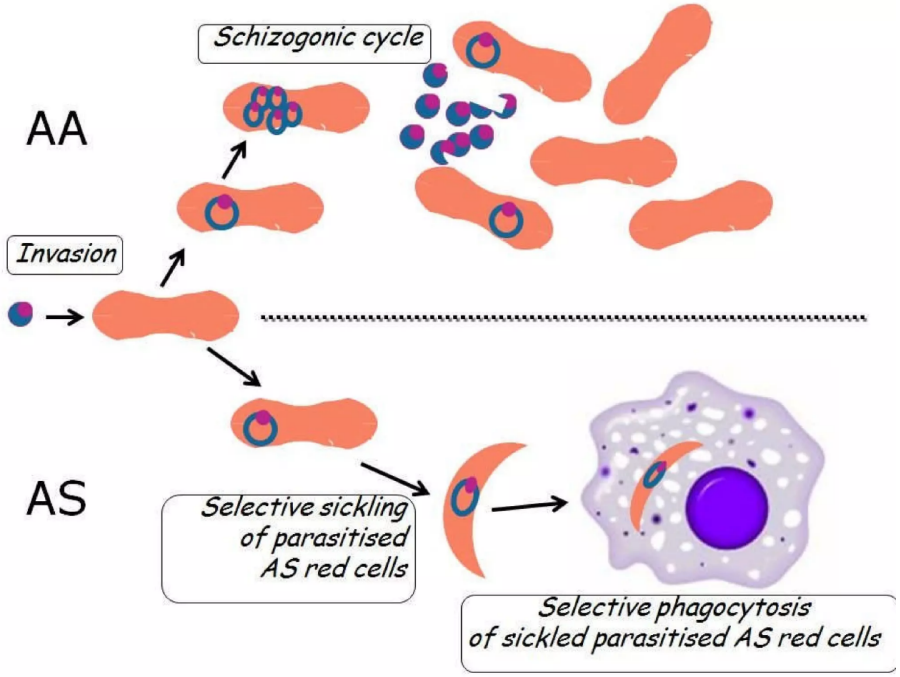
Hb SS

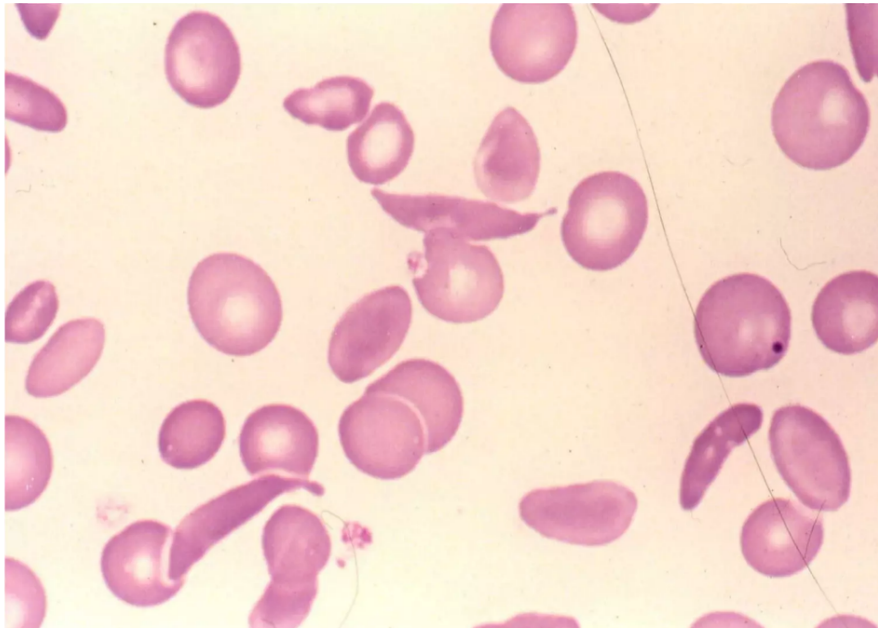


Hb SC



SICKLING AND MALARIA





DIAGNOSIS

TABLE 98-2 Common Sickle Hemoglobinopathies

GENOTYPE	CLINICAL ABNORMALITIES	HEMOGLOBIN LEVEL, g/L (g/dL)/MCV, fL	HEMOGLOBIN FRACTIONS (%)	
Sickle cell trait (HbAS)	8% of African Americans; hematuria, papillary necrosis, hyposthenuria, increased incidence of chronic kidney disease; 2–4 times increased VTE risk; ? stroke; splenic infarction at altitude; rhabdomyolysis	Normal	HbA: 60–70 HbS: 30–40 Percent HbS dependent on presence or absence of α thalassemia	
Sickle cell anemia (HbSS)	Vasoocclusion related: pain, acute chest syndrome, osteonecrosis, splenic infarction Hemolysis related: stroke, pulmonary and systemic vasculopathy, nephropathy, leg ulceration gallstones, priapism, leg ulcers	70–100 (7–10)/80–100	HbS: >75 HbF: 2–25 HbA_2: 3–4	Severe
HbS-β^0 thalassemia	Rate of complications similar to HbSS	80–100 (8–11)/60–85	HbS: >75 HbF: 2–15 HbA_2: 5–6	Severe
HbS-β^+ thalassemia	Rate of complications about half the rate of HbSS depending on percent HbA	100–140 (10–14)/70–80	HbS: 60–90 HbA: 5–40 HbF: 1–10 HbA_2: 5–6	Moderate
Hemoglobin SC disease (HbSC)	Nearly asymptomatic to severe disease; about half the rate of complications as HbSS. Increased risk of retinopathy AVN	100–140 (10–14)/70–100	HbS: 50 HbC: 50	Moderate
HbSE	Resembles clinically HbS-β^+ thalassemia; symptoms delayed; often Asian/Indian ancestry	90–130 (9–13)/65–75	HbS: 65 HbE: 35 HbF: 1-5	
HbSS-α thalassemia	Present in 30% of HbSS; phenocopies HbS-β^0 thalassemia; similar to HbSS but with fewer strokes and leg ulcers and less pulmonary vascular and renal disease	80–100 (8–11)/60–85	HbS: >75 HbF: 2–15 HbA_2: 4–5	Severe
HbS-HPFH	Most common genotype is due to large *HBB* deletions and is asymptomatic	110–140 (11–14)/70–80	HbS: 70 HbF: 20–30 HbA_2: 1–2	

DIAGNOSIS

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Severe

DIAGNOSIS

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Severe

Moderate

DIAGNOSIS

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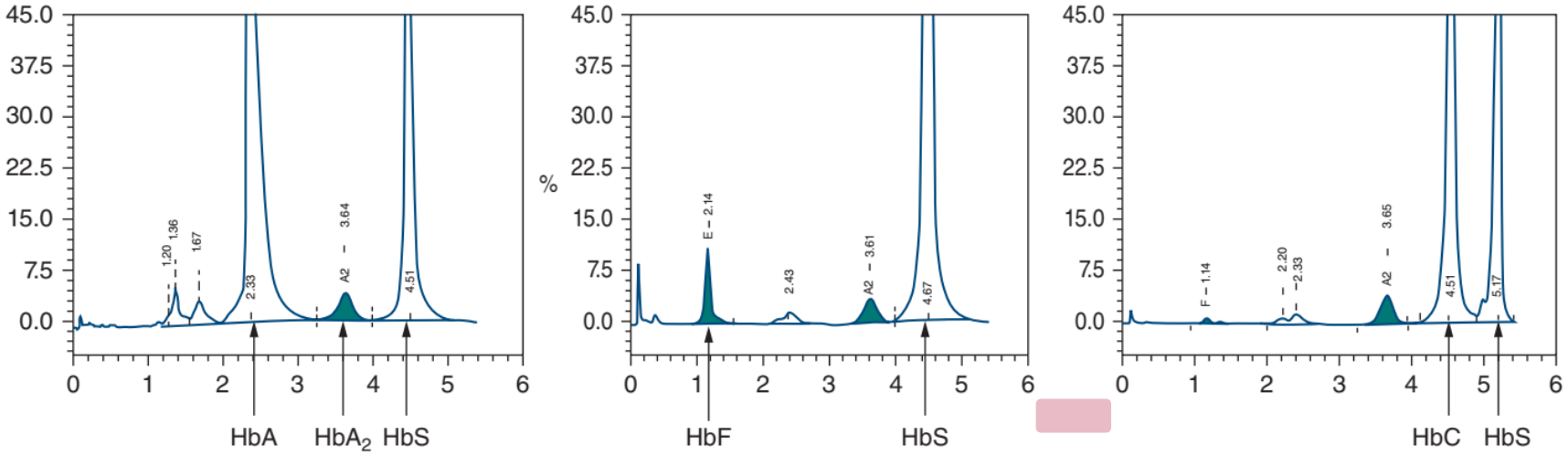
HbS-HPFH	Most common genotype is due to large *HBB* deletions and is asymptomatic	110–140 (11–14)/70–80	HbS: 70 HbF: 20–30 HbA_2: 1–2

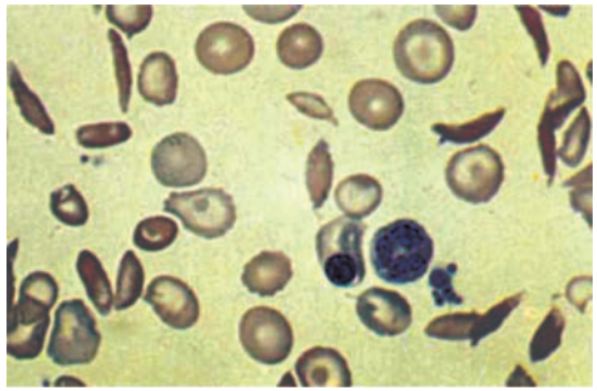
AVN

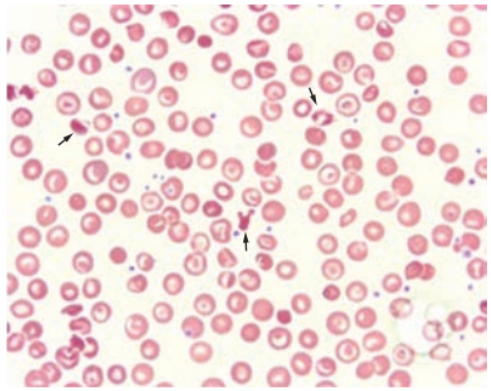
Moderate

Severe

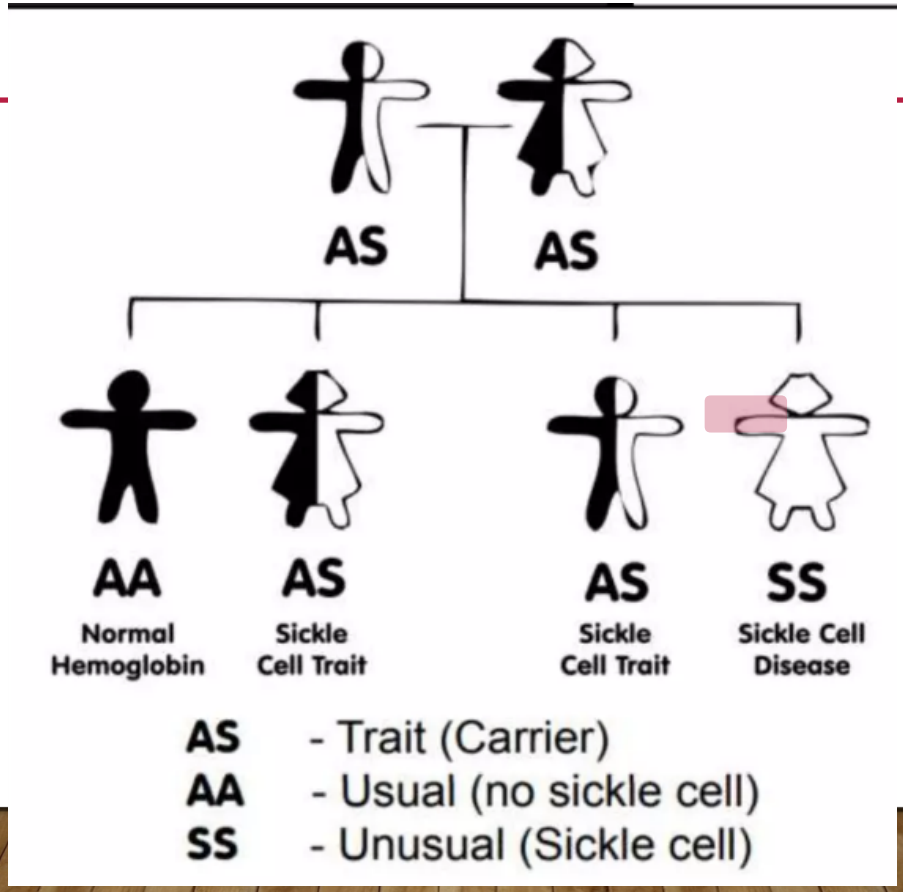
DIAGNOSIS


45.0
37.5
30.0
22.5
15.0
7.5
0.0
%
0 1 2 3 4 5 6
1.20
1.36
1.67
2.33
A2 – 3.64
4.51
HbA
HbA2
HbS
E – 2.14
2.43
A2 – 3.61
4.67
HbF
HbS
F – 1.14
2.20
2.33
A2 – 3.65
4.51
5.17
HbC
HbS



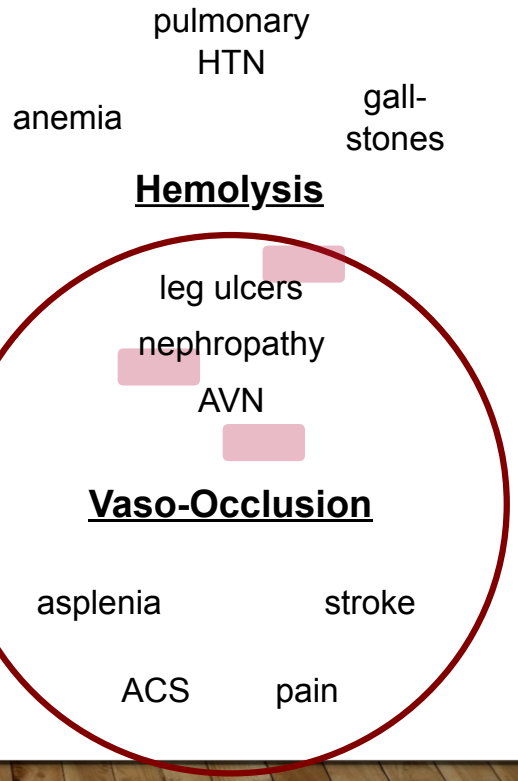


INHERITANCE



MANIFESTATIONS OF SCD

- Chronic anemia
  - Hemolysis
  - Jaundice
  - Cholelithiasis
- Acute complications
  - Pain, priapism, stroke
  - Acute chest syndrome
  - Splenic sequestration
- Chronic organ damage
  - Spleen, brain
  - Kidneys, lung, bones, eyes



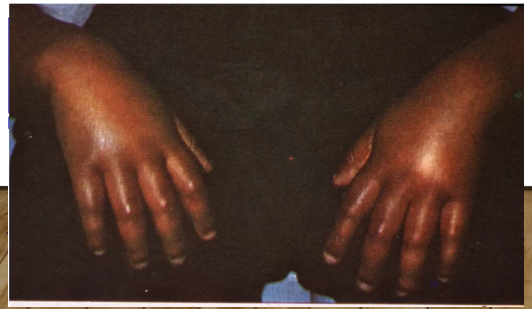
SICKLE CELL TRAIT

- Main Hbs – A>S ; S <50%
- Hematologic parameters – normal
- Associations
  - Microscopic hematuria
  - Renal papillary necrosis (gross hematuria)
  - Isosthenuria
  - Increased risk of chronic kidney disease
  - Increased risk of VTE
  - Splenic infarction (altitude or depressurized flight)
- Generally considered a benign condition
- Exertional heat illness / rhabdomyolysis / death
  - Sudden death described after periods of extreme physical exertion.
  - Exact etiology unclear
  - Hydration

ACUTE PAINFUL EPISODES

- Usually symmetric and stereotypical for each patient
- Most common acute event in SCD

- Triggers of pain often not identified or may be infections or dehydration
- Often accompanied with Hb ↓ and WBC↑
- No relation to reticulocyte or ISCs



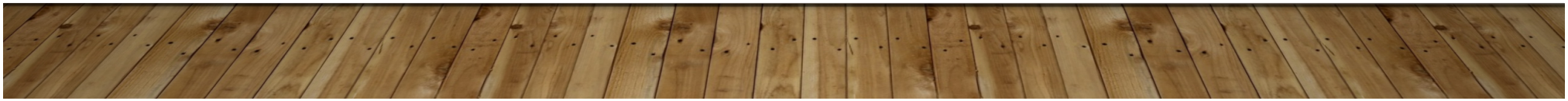
- Management
  - NSAIDs and oral opiates (at home)
  - Fixed dose frequent IV opioids
  - Correct dehydration (half saline)
  - Incentive spirometry to prevent ACS
  - Laxatives (opioid

ACUTE CHEST SYNDROME (ACS)

- Acute pulmonary illness
  - Radiographic pulmonary infiltrate
  - Chest pain, cough, fever
  - Not apparent in 30-60% at time of hospitalization
- Significance
  - May be mild and transient in the very young children with viral infection
  - Common cause of hospitalization
  - Can be fatal (multilobe)
- Inciting Causes
  - Infection (viruses, Mycoplasma, Chlamydia, S. pneumoniae)
  - Pulmonary vascular occlusion
  - Hypoventilation/atelectasis
  - Pulmonary edema

- **Empiric antibiotics**
- **Transfusion**
  - **Often not needed for young children with mild disease**
  - **Simple**
  - **Exchange (severe disease)**

    acute anemia, Plt ↓, WBC>20,000
- **Supportive Care**
  - **Correction of hypoxemia <95%**
  - **Maintenance of normal hydration**
  - **Asthma is very common**



OSTEONECROSIS

- Most often affects hips bilaterally
- Common in HbSC disease
- Loss of function is often the final stage, especially in the hips

- MRI can detect the earliest stages

- Physical therapy and NSAIDs provide some relief
- Oral opioids are sometimes required
- Joint replacement can restore lost mobility and relieve pain

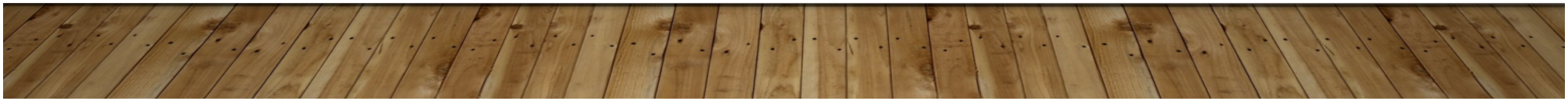


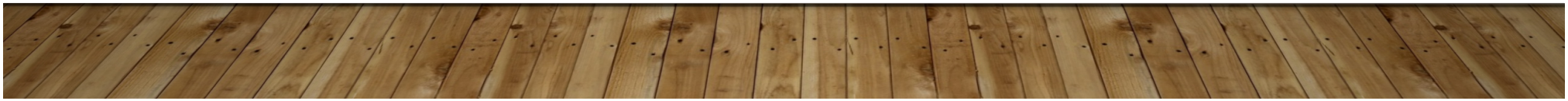
TABLE 98-3 Complications of Sickle Cell Disease

COMPLICATION	INCIDENCE, DIAGNOSIS, AND FEATURES	TREATMENT
Priapism	~30% of males; can be episodic and short duration (stuttering); severe episodes can cause impotence; associated with markers of hemolysis	Many unproven therapies including α-adrenergic agonists, stilbesterol; consult urology for therapy, which is time-critical
Stroke and silent infarction	10–15% of all cases; infarction in early childhood into adulthood; hemorrhagic in adults; neurocognitive abnormalities in adults even without apparent stroke; associated with markers of hemolysis	Transcranial Doppler screening in children aged 2–16; transfusion for at-risk patients; hydroxyurea
Gallstones/surgery	~40% of patients; bilirubin levels and stones related to polymorphisms of *UGT1A*; in surgery requiring general anesthesia, simple preoperative transfusion to a hemoglobin of 10 g/dL is recommended	If asymptomatic, usually let be; otherwise, laparoscopic cholecystectomy
Hepatic disease	>80% of patients have hepatomegaly; intrahepatic cholestasis can have bilirubin ~100 mg/dL; viral hepatitis, iron overload, RBC sequestration, extrahepatic cholestasis also contribute	Exchange transfusion for intrahepatic cholestasis; transplant for end-stage liver failure
Nephropathy	~30% of adults age >30 years; hyperfiltration in children, renal failure in adults; early albuminuria, later nephrotic-range proteinuria; associated with markers of hemolysis	Screen for microalbuminuria by age 10 years; avoid NSAIDs; use ACE inhibitors or receptor antagonists for albuminuria; erythropoietin for symptomatic anemia; dialysis or transplant for renal failure
Lung/pulmonary hypertension	Restrictive disease; asthma common; 5–10% have pulmonary hypertension by right heart catheterization; 30% have increased TRV that portends poor prognosis; associated with markers of hemolysis	Consult expert pulmonologist; screen yearly by echocardiography measurement of TRV
Retinopathy	30% in HbSC disease, 3% in HbSS,[a] develops in peripheral retina; vitreous hemorrhage and retinal detachment can cause blindness	Screen annually starting at age 10 tears with fluorescein angiography; laser photocoagulation for proliferative disease
Acute anemic episodes	B19 parvovirus infection, folic acid deficiency, splenic sequestration, delayed hemolytic transfusion reaction with destruction of transfused and sometimes autologous red cells	RBC transfusion if symptomatic; splenectomy if more than one or two episodes of sequestration; anti-parvovirus IgM positive in acute infection, IgG in past infection
Multiorgan failure	Can accompany severe acute chest syndrome; often confused with sepsis and can coexist with sepsis; CNS, liver, muscle, lung, kidney affected	Exchange transfusion, ICU support
Pregnancy	Screening both partners for hemoglobin disorders with risk counseling is critical component of family planning.	All pregnancies are "high risk"; transfuse if sickle cell events increase, if previous miscarriage, multiple fetuses

LEG ULCERS

- Mostly in sickle cell anemia and HbS-β0 thalassemia
- Tropical and subtropical areas
- Can be extraordinarily painful

- Long-standing, recurrent large ulcers are difficult to treat
- Wet-to-dry dressings and Unna boots are



HYDROXYUREA: PREVENTIVE TX FOR ALL

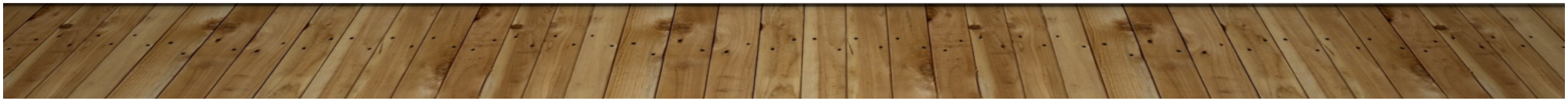
- Mechanism
  - Induction of Hb F
  - Heterocellular effect
- Indication:
  - Hb SS/Sβ0
  - In the 1st year
- Dosing
  - Once daily oral formulation
  - Begin at ~20 mg/kg
  - Increase incrementally up to
- Toxicity
  - Transient, dose-related neutropenia or thrombocytopenia
  - Requires monitoring of CBC
- Efficacy
  - Decreases frequency of pain, ACS, hospitalizations, transfusions
  - Increases Hb

VOXELOTOR

- Mechanism
  - Decreases P50
  - Increases Hb O2 affinity
  - Pancellular
- Dosing
  - Once daily oral formulation
  - 1500 mg/d

- Toxicity
  - ???
- Efficacy
  - Decreases frequency of veno-occlusive events
  - Increases Hb
  - Decreases hemolysis

➢ **Can be added to hydroxyurea**

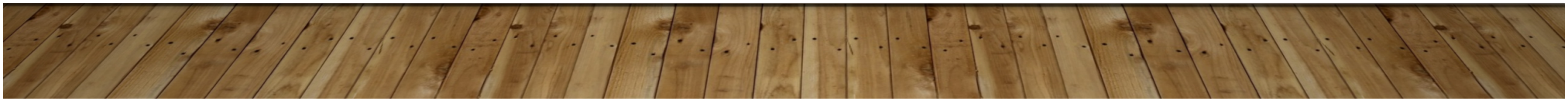


CRIZANLIZUMAB

- Mechanism
  - Monoclonal Ab
  - P-selectin inhibitor
  - Prevents HbS interaction with endothelium & WBCs
- Dosing
  - Monthly IV injections

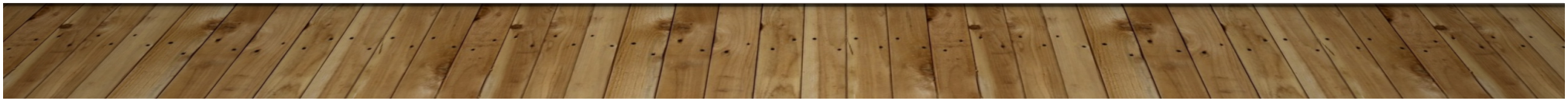
- Toxicity
  - ???
- Efficacy
  - Decreases acute pain episodes

➢ **Can be added to hydroxyurea-Voxelotor**



L-GLUTAMINE

- Mechanism
  - Reduces oxidative stress (?)
- Dosing
  - Monthly IV injections
- Toxicity
  - ???
- Efficacy
  - Decreases acute pain episodes
  - Reduces hospitalization

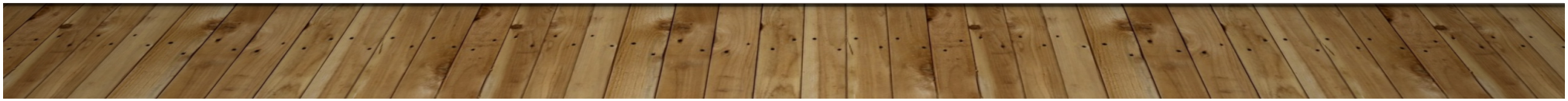


TRANSFUSION THERAPY

- Simple transfusion ("top-up")
  - Severe symptomatic anemia
  - Correct Hb to 10 g/dL before surgery
- Exchange transfusion
  - Acute stroke
  - Severe ACS (multilobar/hypoxic)
  - MOFS

- Main complications
  - Hyperviscosity
  - Iron overload
  - Alloimmunization
  - Hyperhemolysis
  - Delayed hemolytic reactions

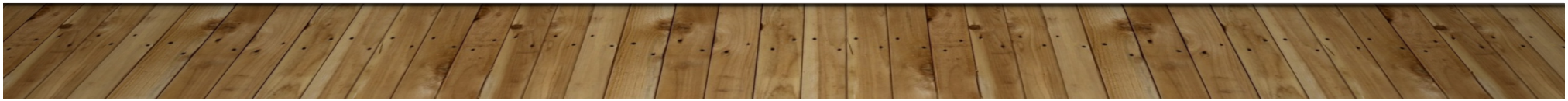
➢ **Matching before 1st transfusion to Rh (C/c, E/e, D) , ABO , K**



STEM CELL TRANSPLANTATION FOR SCD

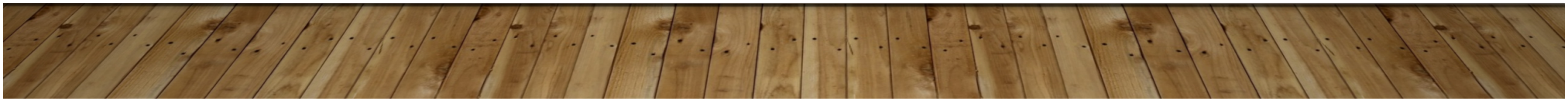
- SCT is only curative therapy for SCD

- Indicated for all patients with suitable donor
- HLA-matched sibling donors are limited
- Ongoing research to expand donor choices and reduce toxicity



PREVENTIVE MEASURES

- Cord blood screening for sickle cell disease is done in many countries
- Transcranial Doppler screening beginning at age 2 years and repeated annually until age 16 years
- Prophylactic penicillin (125 mg for children younger than 3 years; 250 mg for children 3 years and older) twice daily until age 5 years
- Vaccination with pneumococcal vaccines
- Folic acid, 1 mg daily to prevent megaloblastic erythropoiesis
- Antenatal diagnosis using chorionic villus sampling
- Screen partners if HbS or β thalassemia trait



GENE THERAPY