Interpretation & Management of Hematologic Disorders Identified on Newborn Screening

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Objective

Hematologic conditions diagnosed by newborn screening

Diagnosis and management of

- Hemoglobinopathies
  - α and β thalassemia
  - Sickling disorders
- G6PD deficiency

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Outline

Background:

- Hemoglobin: structure and development
- Hemoglobinopathy: nomenclature and Dx

Common hemoglobinopathies and management

- Thalassemia :Alpha and beta thalassemia
- Sickle cell disease

G6PD deficiency

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Hemoglobin

Heme + Globin

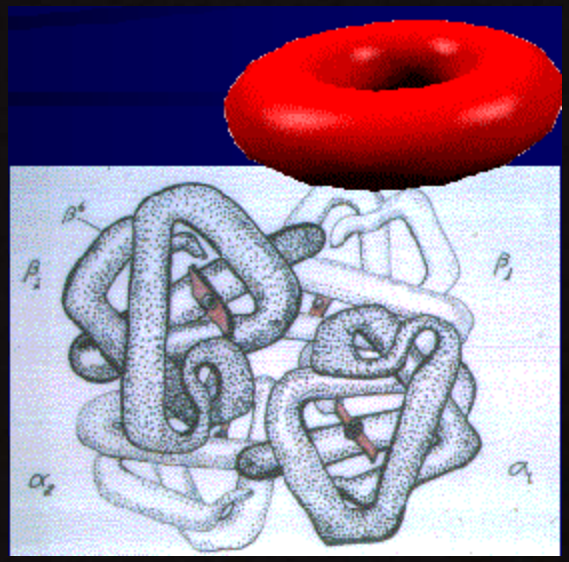
Four globin chains:

- 2 α like globin chains
- 2 β like globin chains

Four heme group

- One per globin chain

Tetramer structure



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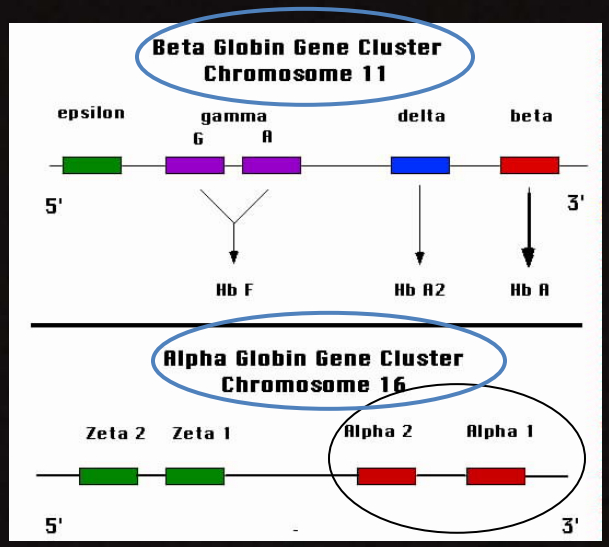
Hemoglobin: Names to know

HbA	Adult Hb	$\alpha_2 \beta_2$
HbA2	Minor adult	$\alpha_2 \delta_2$
HbF	Fetal Hb	$\alpha_2 \gamma_2$
Hb Barts	Abnormal Hb	γ_4
Hb H	Abnormal Hb	β_4



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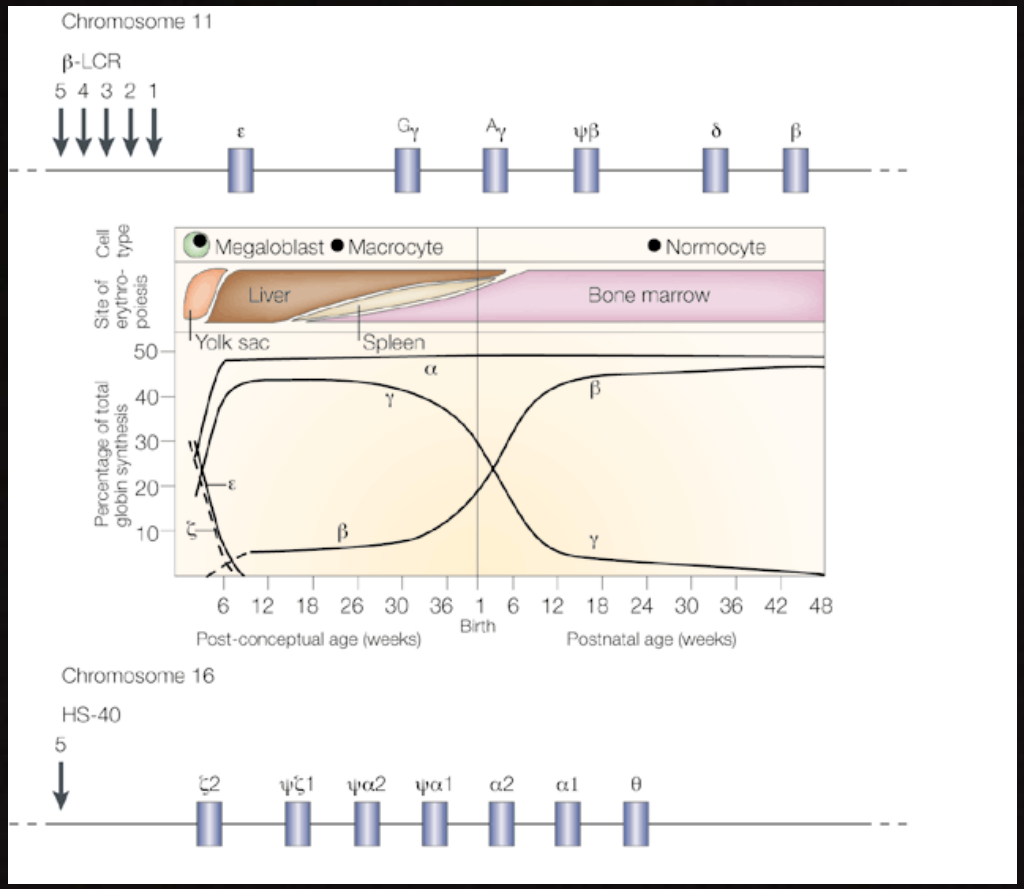
Hemoglobin switching: fetal to adult



- Hemoglobin F (α_2 γ_2) is the predominant hemoglobin at birth
- Hemoglobin Barts (γ_4) disappears with increasing hemoglobin A (α_2 β_2): A normal developmental phenomenon

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Newborn screening

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It is a law!

Every state in the U.S. has program to screen newborns for inherited disorders
Number of tests may vary by states but hemoglobinopathy screen is universal

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Thalassemia and other hemoglobinopathies: Global distribution

- Frequency of the mutant allele depends on the ancestry
- All newborns are screened regardless of race and ethnicity

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Hematologic disorders on newborn screen

Thalassemia: Quantitative Disorders of Hb

- Alpha Thalassemia
- Beta thalassemia

Hemoglobinopathies: Qualitative Disorders of Hb:

- Sickle cell disease: SS, SC, Sickle beta thal
- Other Hemoglobinopathies: C, E
- Variant hemoglobins

Enzymopathy: G6PD deficiency

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Quantitative Disorders (Thalassemias)

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Alpha Thalassemia

Chromosome 16

Genotype	Pattern	Name	Features/ Management
αα/αα	FA	Normal	
αα/α-	FA Barts	Silent carrier	Genetic counseling
αα/- - α-/α-	FA Barts	Alpha thal trait (minor)	Mild anemia/microcytosis Check for iron deficiency
α -/- -	FA with Barts > 25%	Hemoglobin H disease (intermedia)	Moderate to severe anemia, hepatosplenomegaly Hb H inclusion May need PRBC transfusions
- -/- -	≈ 100% Hb Barts	Hydrops fetalis (major)	Fetal hydrops and demise Intrauterine PRBC transfusions HSC transplant

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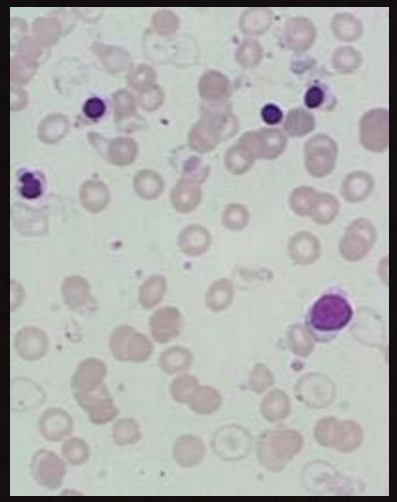
Beta Thalassemia

Chromosome 11

Genotype	Name	Features
β/β	Normal	
β/β^0 β/β^+	Beta thal trait (minor)	Normal count in neonate Elevated F and A_2 Mild anemia, microcytosis
β^+/β^+ β^+/β^0	Beta thal Intermedia	Normal Count in neonate Hypochromia and microcytosis Elevated F and A_2 Variable hepatosplenomegaly Intermittent transfusion
β^0/β^0	Beta thal major	Normal counts in newborn F only pattern of electrphoresis Sever hypochromic microcytic anemia, hepatosplenomegaly Lifelong transfusion/ HSC transplant

Clinical phenotype varies in thalassemia:

vs.



Number of genes affected or the type of mutation typically dictate the clinical phenotype

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Qualitative disorders (Hemoglobinopathies)

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Hemoglobinopathy screen

All detected hemoglobin are reported

Reported in the order of amount present

FAS means HbF > HbA >HbS

FAS (sickle trait) ≠ FSA (sickle beta plus thal)

Variant hemoglobins

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Newborn screen: Common patterns

Pattern	Interpretation
FA	Normal
FAS	Sickle cell trait
FS	Sickle cell anemia (SS) or sickle beta zero thal
FSA	Sickle beta plus thalassemia
FSC	Sickle-Hb C (SC) disease
FAV	Trait or heterozygous for Hb variant

α thal/ hemoglobin Bart can coexist with β globin mutations
Occasionally DNA analysis may be needed for diagnosis

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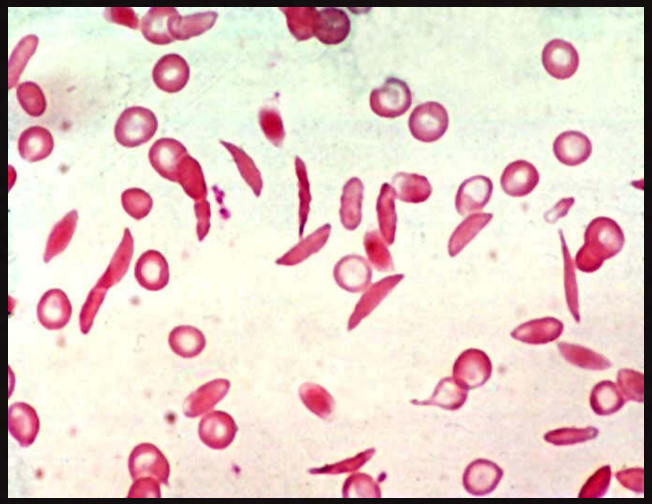
Sickling disorders:



Sickle cell disease : group of diseases with presence of sickle gene: HbSS, HbSC, $S\beta^{+}$thal, $S\beta^{0}$thal, SD Punjab, SO Arab

Sickle shaped RBCs

Autosomal recessive

Sickle cell trait (AS): 1:10

Sickle cell disease 1:500 in US African Americans

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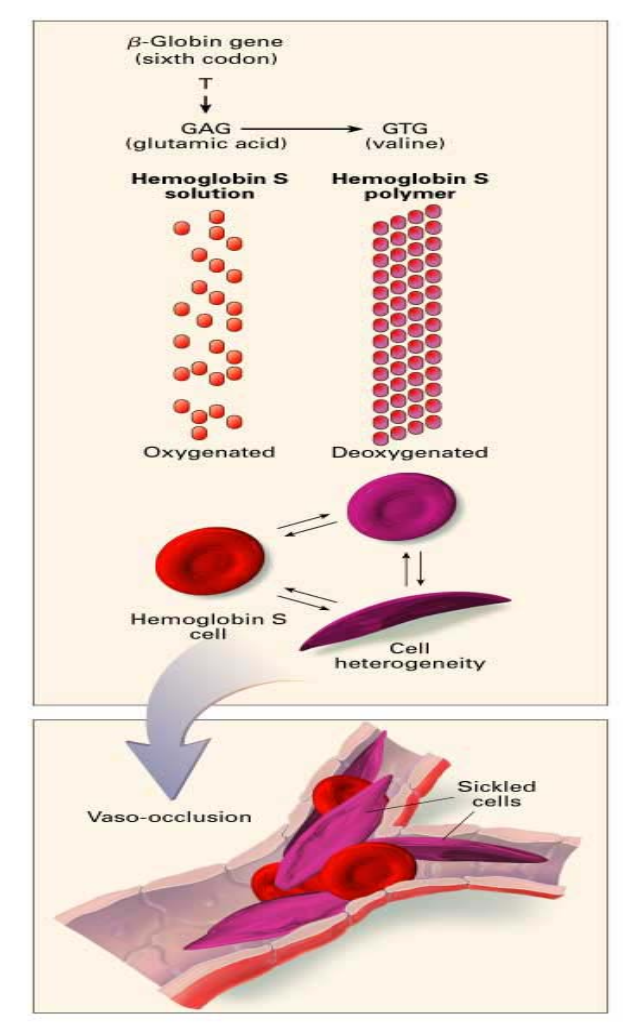
Pathophysiology



A **GAG to GTG substitution** → replacement of glutamic acid residue by valine.

Upon deoxygenation HbS polymerization→**sickling** → **vaso-occlusion**.

Early manifestations: dactylitis and splenic sequestration

Steinberg MH, NEJM 1999

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Dactylitis

- Often the first symptom of SCD (6 mo-2 y)
- Painful swelling of hand and feet. Infarction of bone marrow due to occlusion of blood supply.
- Rx: Hydration, pain management

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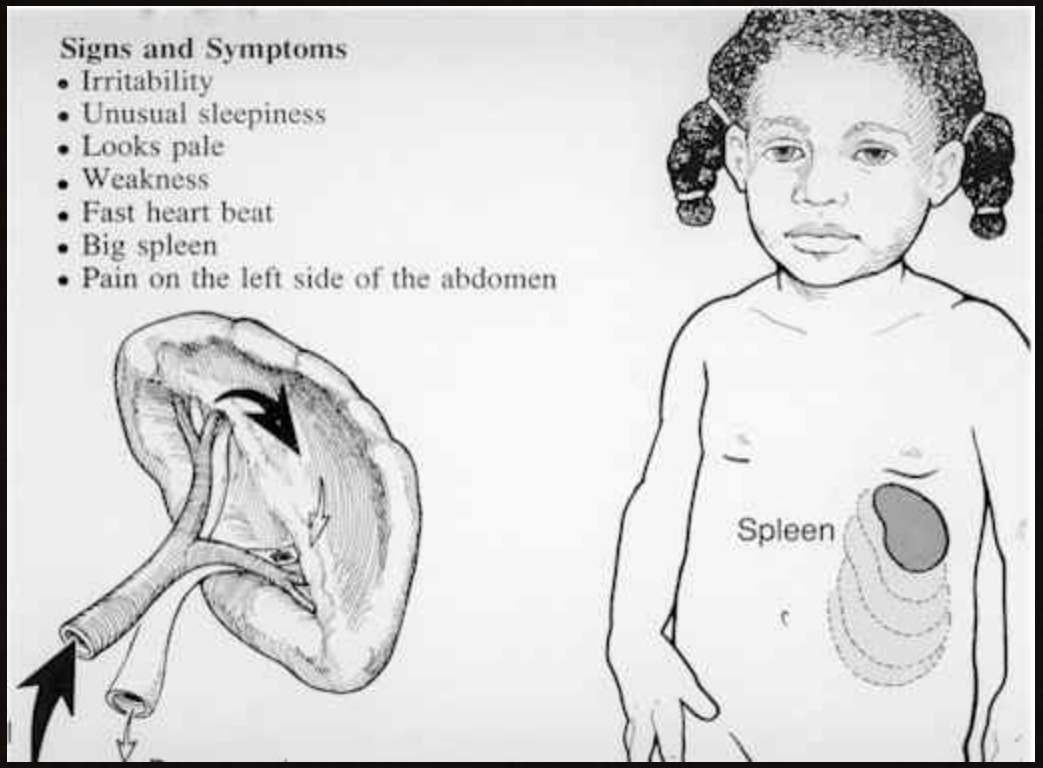
Splenic sequestration



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After the newborn screening

Sickle cell trait (AS):

- Genetic counseling

Sickle cell disease: SS, SC, $S\beta^{+}$thal, $S\beta^{0}$thal and other sickling disorders

- Penicillin prophylaxis: at least up to age 5 years
  - 125 mg PO BID for < 3 years;
  - 250 mg PO BID ≥ 3 years
- Hematology visit /confirmatory testing
- Multidisciplinary infant sickle cell clinic

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SCD Health Maintenance

- Education and counseling:
  - Pain and fever management
  - Spleen palpation
  - Penicillin prophylaxis
  - School and IEP
  - Physical activity
- Immunizations:
  - All recommended immunizations
  - 23 valent pneumovax at 2 and 5 years
  - MCV4 two doses (other meningococcal vaccines per ACIP)
  - Influenza vaccine

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SCD Health Maintenance

Screening:

- Annual transcranial doppler to evaluate stroke risk (Hb SS and sickle β^0 thalassemia) starting at 2 years of age
- Annual eye evaluation for retinopathy starting 10 years (Hb SC patients are at higher risk)
- Examination of hip for avascular necrosis
- Growth and development; neuropsych evaluation
- Mental health assessment

Disease modifying therapies as indicated:

- Hydroxyurea
- Chronic blood transfusion
- Hematopoietic stem cell transplant

Improved outcome for individuals living with SCD

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G6PD deficiency

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G6PD deficiency

Most common red cell enzyme disorder

X linked inheritance

↓ G6PD → ↓ NADPH production (free radical detoxifcation)

Hemolysis in response to oxidative stress: (ex. infections, drugs, fava beans) → anemia, jaundice

Heinz bodies and blister cells on peripheral smear

- Clinical features ranges: Asymptomatic/ neonatal jaundice/ hemolysis

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G6PD deficiency: Classes

Classes of G6PD Enzyme Variants

CLASS	LEVEL OF DEFICIENCY	ENZYME ACTIVITY	PREVALENCE
I	Severe	Chronic nonspherocytic hemolytic anemia in the presence of normal erythrocyte function	Uncommon; occurs across populations
II	Severe	Less than 10 percent of normal	Varies; more common in Asian and Mediterranean populations
III	Moderate	10 to 60 percent of normal	10 percent of black males in the United States
IV	Mild to none	60 to 150 percent of normal	Rare
V	None	Greater than 150 percent of normal	Rare

Am Fam Physician. 2005 Oct 1;72(7):1277-1282

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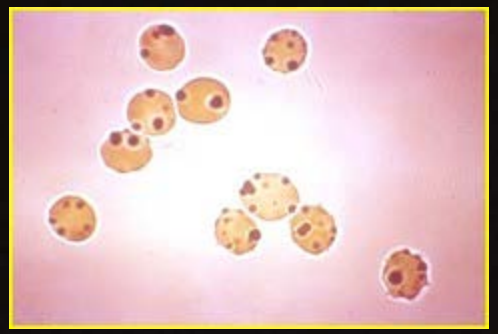
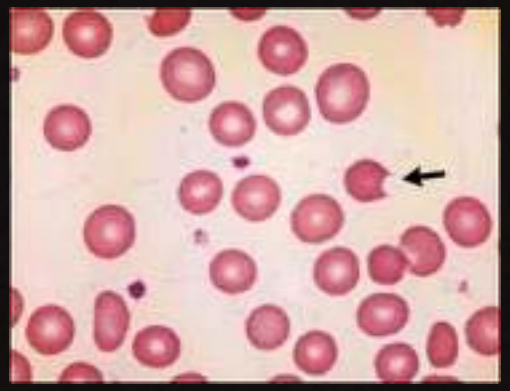
G6PD deficiency





Denatured Hemoglobin
Heinz bodies
“Blister cells” on smear

Fava beans

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G6PD deficiency

Education and counseling:

- Risk factors
- Drugs and other precipitating causes to avoid
- Sign and symptoms of acute hemolysis and anemia (change in urine color, pallor)

Management:

- Ranges from observation to red cell transfusion

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Conclusion

Newborn screen is an important tool in identifying common inherited hematologic disorders

Early diagnosis is crucial for appropriate management

Collaboration between the primary physician and the hematologist is the key to improve the outcome of affected children

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Thank you

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