Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Hemoglobin disorders

Oyebimep Adesina, MD, MS

Assistant Professor of Medicine (Hematology)
University of California Davis School of Medicine

adesina@ucdavis.edu

DISCLOSURES

Research funding:

- Doris Duke Charitable Foundation
- NHLBI
- NICHD

ABIM Hematology exam blueprint

- **Thalassemias**
  - β-thalassemia
  - α-thalassemia
  - Hemoglobin E disorders

- **Sickle cell disorders**
  - Sickle cell trait
  - Sickle cell anemia (hemoglobin SS disease)
  - Hemoglobin SC disease and C hemoglobinopathy
  - Sickle cell-β^0 and sickle cell-β^+ thalassemias

- **Non-sickle hemoglobinopathies**

- **Educational resources**

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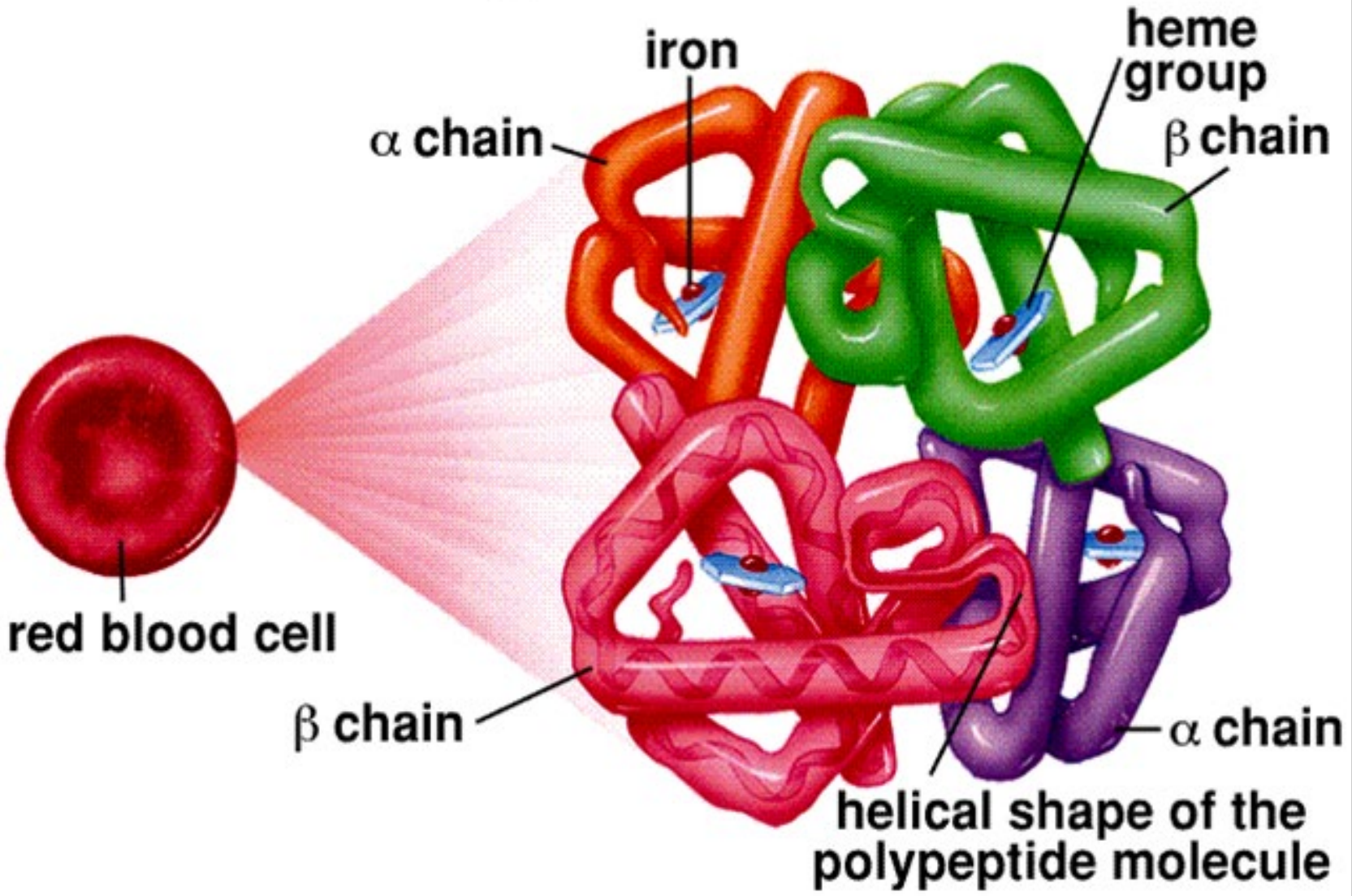
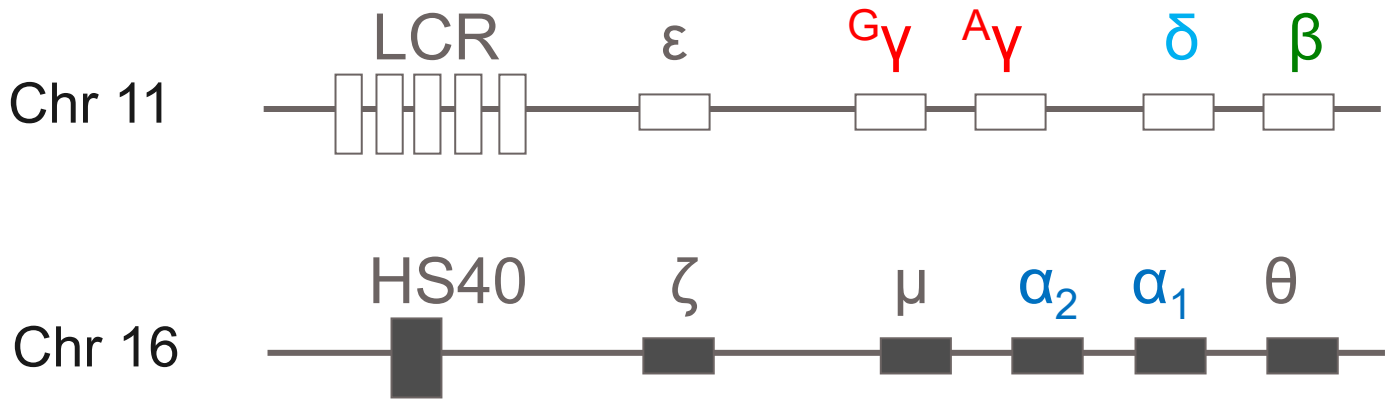
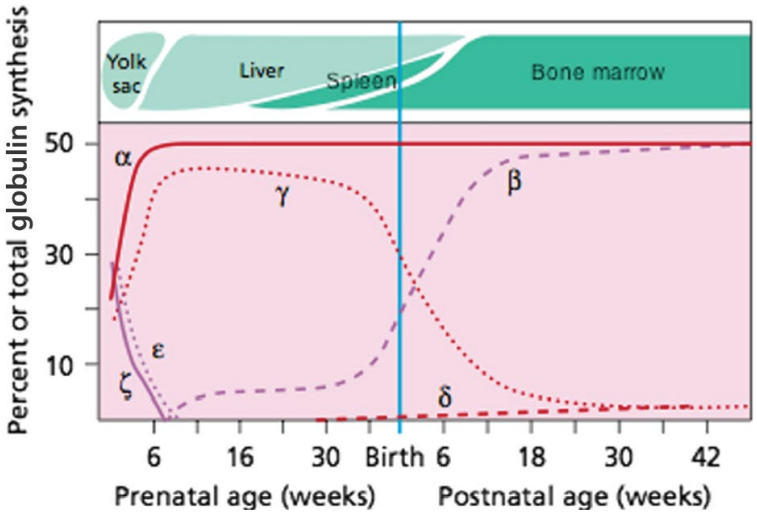
Hemoglobin Molecule



Globin genes and hemoglobin variants





Postembryonic hemoglobin species

A	$\alpha_2\beta_2$	(97%)
A2	$\alpha_2\delta_2$	(3%)
F	$\alpha_2\gamma_2$	(<1%)

Adapted from ASH SAP 2013 Chapter 7.

Hemoglobin disorders

- Thalassemias:
- Named after the reduced/absent *structurally normal* globin chain
- α-thalassemia: excess β-chains
- β-thalassemia: excess α-chains

- Hemoglobinopathies:
- Amino acid substitution results in *structurally abnormal* hemoglobin → **Hb S**, Hb C, HbSC, Hb G-Philadelphia, Hb D, Hb O-Arab, etc.

- Thalassemia-hemoglobinopathy:
- HbS-β thalassemia, HbE-β thalassemia, etc.

Genetics of thalassemias

α-thalassemias

- expressed in fetus and at birth
- Predominantly gene deletion(s)

β-thalassemias

- expressed several months after birth (γ-globin → β-globin)
- Predominantly point mutations

β-thalassemias

- **Causative mutations**
  - β^0 (null) = No gene product
  - β^+ = reduced production

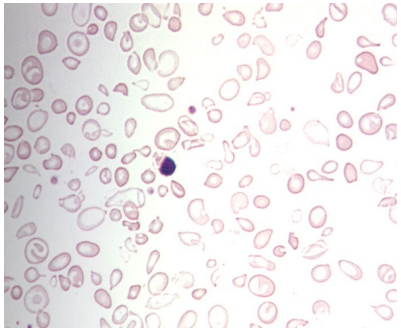
- **Excess α-globin chains → INEFFECTIVE ERYTHROPOIESIS**
  - α-globin aggregates in erythroid precursors → intramedullary death

- **Excess free intracellular iron:**
  - membrane lipid oxidation
  - membrane protein damage

- **Membrane damage → PS* exposure and hypercoagulability**
  - decreased RBC deformability
  - increased clearance from circulation

PS phosphatidylserine

Complications of thalassemias



Impaired α:ß globin ratio

Red cell pathology

Inneffective erythropoiesis

Hemolysis → **Gall stones**

Iron overload

Anaemia

↓ Tissue oxygenation

Erythroid marrow expansion

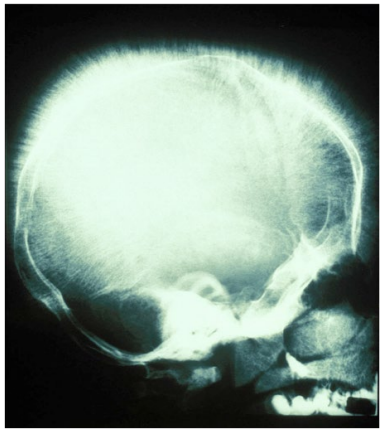
Hypercoagulable state

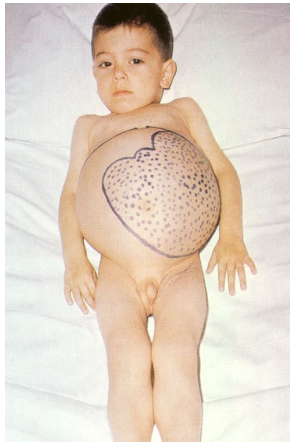
- Diabetes mellitus
- Growth deficiency
- Hypothyroidism
- Hypoparathyroidism
- Hypogonadism
- Hepatic cancer
- Renal disease

- Leg ulcers
- Thrombotic events
- Pulmonary hypertension

- Bone deformities
- Osteoporosis

- Hepatosplenomegaly
- Extramedullary hematopoietic psuedotumors





From Guidelines for the Managements of Nontransfusion dependent Thalassemia. Thalassemia International Federation publication 2013.

Hoffbrand & Pettit Color Atlas of Clinical Hematology; © Harcourt, 2000

Clinical classification of β-thalassemias

Phenotype	Hb (g/dL)	Transfusions	Clinical features	Most common genotype
Thalassemia minor (trait)	**10-12**	**No**	No hemolysis or anemic symptoms, **RBC > 5million**, **HbA2 > 3.5%**	**β^0/β or β^+/β**
Thalassemia intermedia	7-10	+/-	**High Hb F,** bone disease, **transfusion and non-transfusion-related iron overload,** splenomegaly*, pulmonary HTN, leg ulcers	**β^+/β^+ or β^+/β^0**
Thalassemia major	<7	Age < 2 yrs	**>95% HbF**, bone disease, **transfusion** iron overload, splenomegaly*	**β^0/β^0 or β^0/β^+**

*splenomegaly due to increased hemolysis and extramedullary hematopoiesis

β-thalassemia major: current treatment

- **Referral to comprehensive medical center**
  - Hematology, Genetics, Cardiology, Hepatology, Endocrinology, Ob/Gyn
- **Supportive care**
- **RBC transfusions:** typically, 2-3 pRBCs q 3-4weeks
  - pre-transfusion Hb: 9-10.5 g/dL
  - post-transfusion Hb: 12-15g/dL
- **Iron chelation**
  - Initiate **after 10-20 pRBCs or ferritin>1000ug/L**
  - **Single chelator or combination therapy**
  - **Goals:**
    - liver iron concentration (LIC) < 3mg/g
    - cardiac T2* <20ms
      - **Cardiac iron → consider combination therapy (e.g., DFO+DFP)**

DFO Deferoxamine; DFP Deferiprone

Iron chelators

Medication	Brand name	Dose	Route/form	Comments
Deferoxamine (DFO)	Desferal®	50-60mg/kg/d 5-7 days per week	SQ/IV 8-24h	Local reaction, hearing loss, retinopathy, growth delay
Deferiprone (DFP)	Ferriprox®	25-33mg/kg/d q8h	PO (tablets)	Neutropenia, n/v/d, elevated LFTs, arthralgia
Deferasirox (DFX)	Exjade®	20-40mg/kg/d q24h	PO (dispersible)	elevated creat, rash, n/v/d
	Jadenu®	14-28mg/kg/d q24h	PO (tablets or sprinkles)	elevated creat, rash, n/v/d, less diarrhea (no lactose)

β-thalassemia major: current treatment

- **Splenectomy**
  - Indications: transfusions >200-220mL/kg/year; un-transfusable due to alloimmunization, severe cytopenias, symptomatic splenomegaly
  - **less used than before due to complications**
    - post-op pancreatitis, pleural effusion, portal vein thrombosis;
    - long-term risk for sepsis and VTE; need for antibiotic prophylaxis
- **Luspatercept**
  - FDA-approved for transfusion-dependent β-thalassemia (April 2020)
  - Activin receptor ligand trap → improves ineffective erythropoiesis
  - Dose: 1-1.25mg/kg SQ q 3 weeks
  - >33% reduction in transfusion burden in 72% patients
  - AEs: bone pain, headache, asthenia

Piga et al. Blood 2019; 133(12):1279-1289

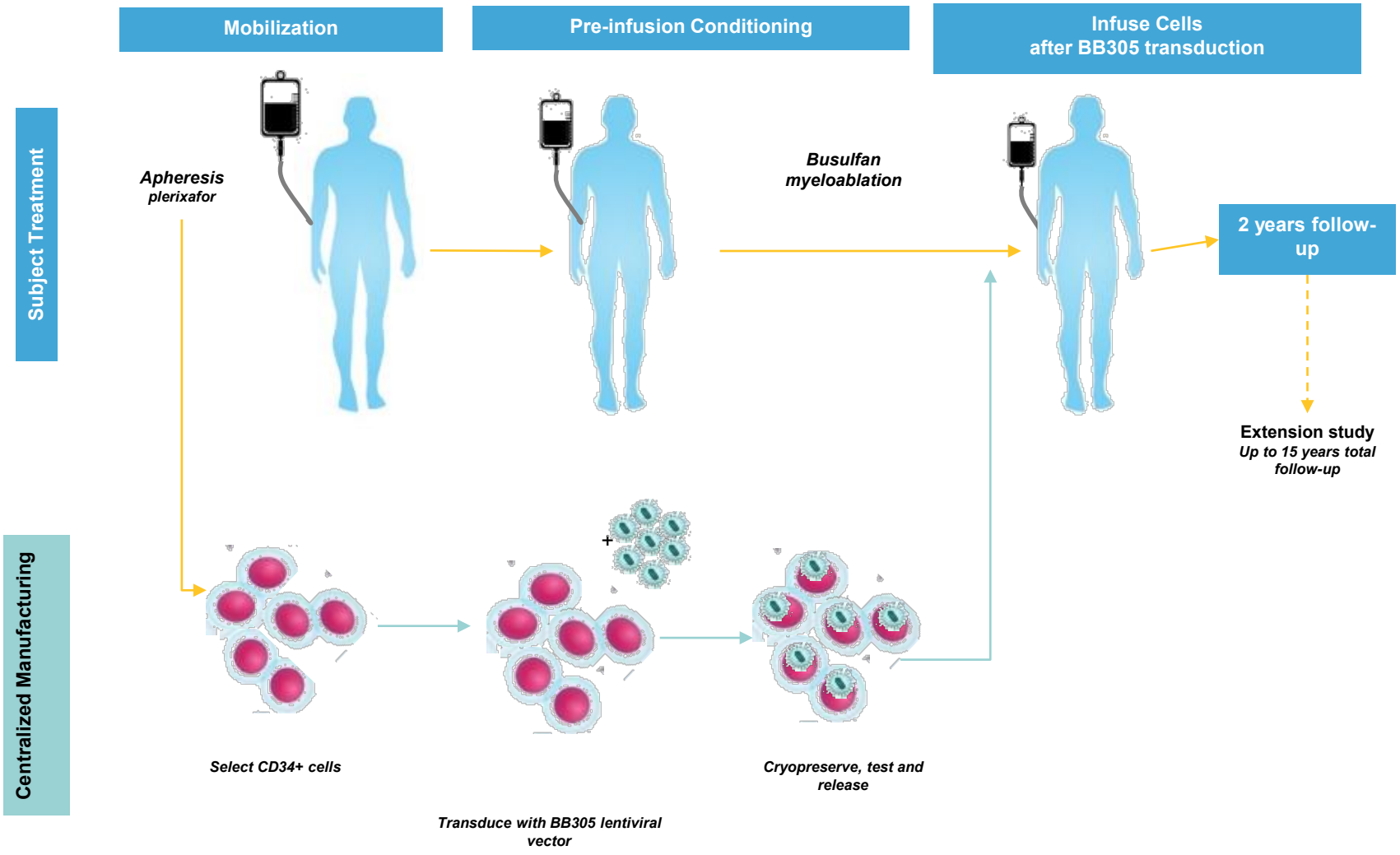
β-thalassemia major: current treatment

- **Allogeneic hematopoietic cell transplantation**
  - Age<14 years; HLA-matched sibling donor; no significant iron overload
  - Pesaro system: predicts post-BMT 3-year OS in children < 16years
  - Adverse factors:
    1. Hepatomegaly >2cm from costal arch
    2. Liver fibrosis on biopsy
    3. Irregular iron chelation
       - Class I: 0 adverse factors → 94%
       - Class II: 1 or 2 adverse factors → 80%
       - Class III: all adverse factors → 61%

- **Investigational: LentiGlobin gene therapy**

  (Thompson et al. N Engl J Med. 2018 Apr 19;378(16):1479-1493)

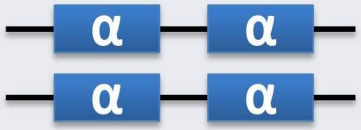
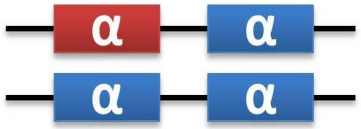
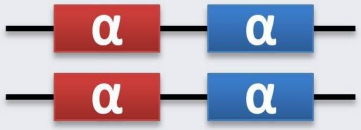
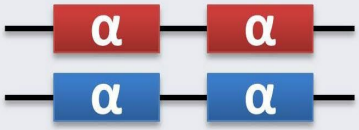
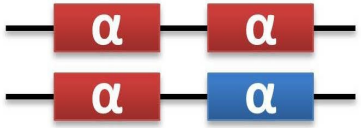
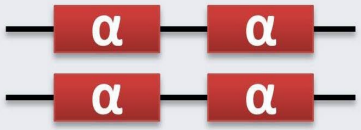
LentiGlobin gene therapy for hemoglobin disorders



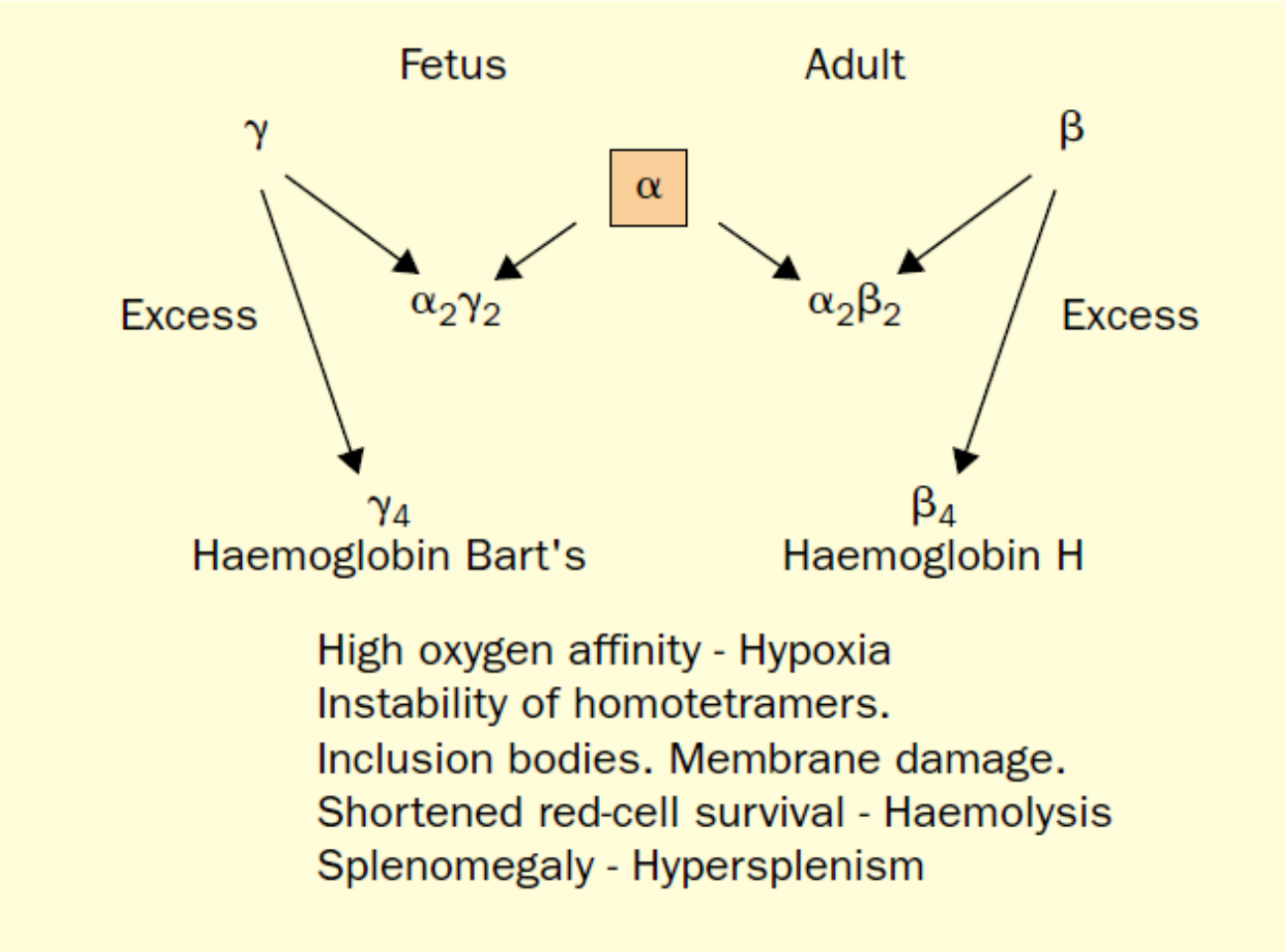
Courtesy of Dr. Kanwaldeep Mallhi (University of Washington/Seattle Children's/Fred Hutch Cancer Research Center)

Alpha thalassemia genetics

Chromosome 16

Normal		**Normal αα/αα**
Carrier: Asymptomatic No abnormalities (labs WNL or isolated microcytosis)		**α⁺ trait: α-/αα**
α-thal minor: Asymptomatic Mild microcytic anemia	**homozygous α⁺ trait** -α/-α  or **α⁰ trait** --/αα 	
Hb H Disease: Symptomatic Hemolytic and Microcytic anemia Splenomegaly		**Hb H disease --/-α**
Incompatible with Life Hydrops Fetalis		**Hydrops fetalis --/--**

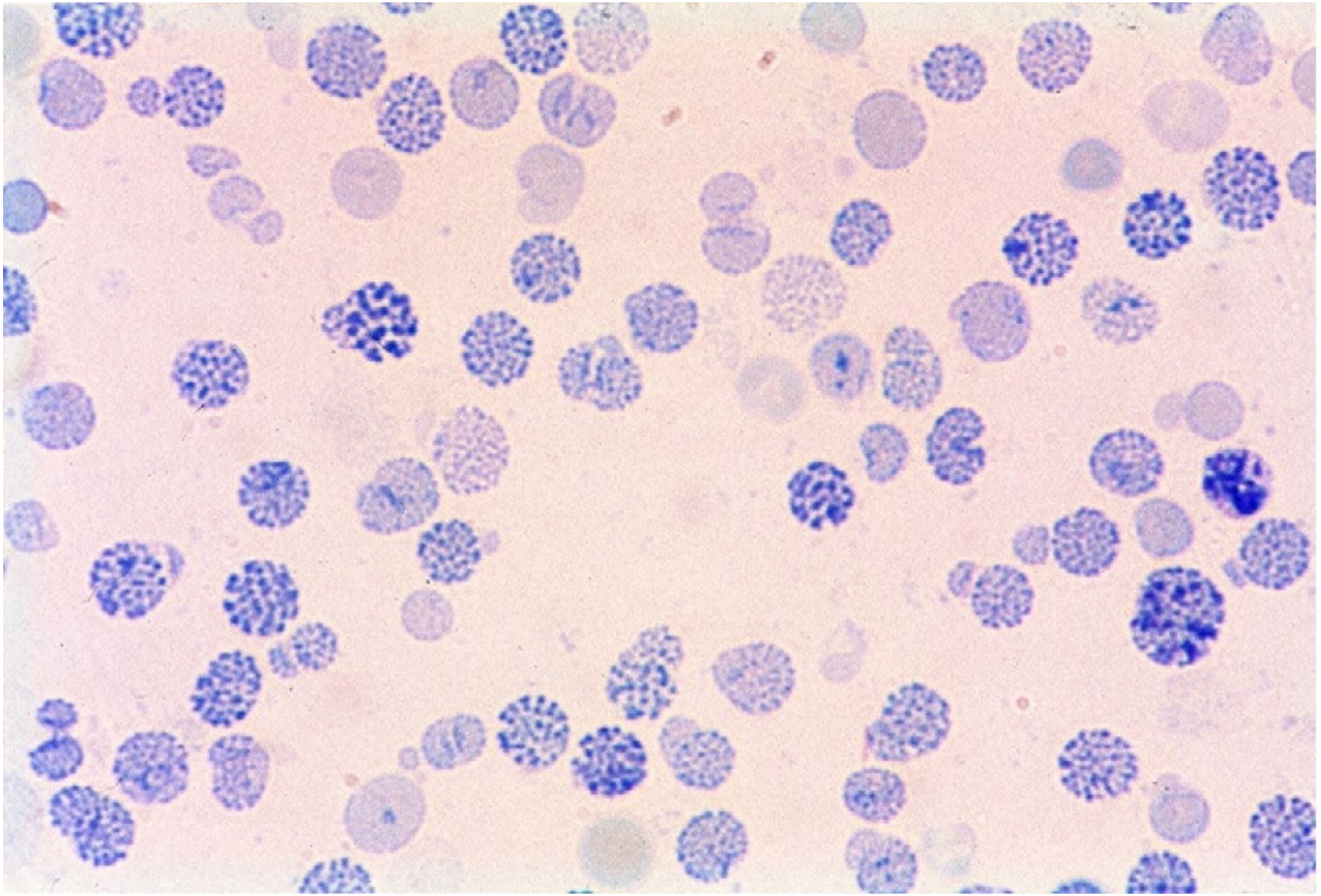
Pathophysiology of alpha thalassemias



- excess of γ-like globin chains – Hb Bart's
- excess of β-like globin chains – Hb H

DJ Weatherall, AB Provan. *The Lancet*, Volume 355, Issue 9210, 2000, Pages 1169-1175

Peripheral blood smear: Hb H disease



DJ Weatherall, AB Provan. *The Lancet*, Volume 355, Issue 9210, 2000, Pages 1169-1175

Alpha thalassemia - continued

- **If α-thalassemia trait (carrier state) is suspected:**
  - Consider compatible ethnicity and clinical picture
  - no hemolysis, family history of HbH or hydrops

- **Rule out the following conditions:**
  - Iron deficiency
  - β thalassemia trait
  - Newborn screening: may show Hb Bart's or HbH
  - Adults: confirmed if positive for HbH inclusions in peripheral blood or confirm with genetic testing for deletions

Unusual alpha thalassemias

- **α-thalassemia-mental retardation syndromes**
  - ATR-16 syndrome : large deletions in α-globin genes on chromosome 16
  - ATR-X syndrome: mutations in ATRX gene (chromatin-associated protein)

- **α thalassemia associated with myeloid malignancy (ATMDS)**
  - acquired α-thalassemia mostly in MDS, very rarely MPN or AML
  - ATRX mutation with low MCV/MCH; HbH inclusions can be present

Treatment for alpha thalassemias

- **Hb Bart's hydrops fetalis (--/--)**
  - Intrauterine transfusions → chronic transfusions and chelation
  - screening, genetic counseling in high-risk populations
  - hematopoietic cell transplantation (in certain cases)

- **HbH disease (α-/--)**
  - Splenomegaly may lead to hypersplenism
  - Hemolytic crises →RBC transfusions +/-iron chelation
  - Complications: gallstones, leg ulcers

- **Mild α thalassemia (α-/α- or αα/--)**
  - genetic counseling
  - avoid unnecessary iron supplementation

ABIM Hematology exam blueprint

- **Thalassemias**
  - β-thalassemia
  - α-thalassemia
  - Hemoglobin E disorders

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  - Sickle cell anemia (hemoglobin SS disease)
  - Hemoglobin SC disease and C hemoglobinopathy
  - Sickle cell-β^0 and sickle cell-β^+ thalassemias

- **Non-sickle hemoglobinopathies**

- **Educational resources**

Hemoglobin E

- **Thalassemic hemoglobinopathy**
  - amino acid substitution *HBB* p.Glu26Lys
  - decreased β^E-mRNA production
  - precipitation of α-globin chains in cytoplasm of erythroid precursors and RBCs
  - increased oxidant stress

- **2nd most prevalent Hb variant in the world**
  - 30 million worldwide with > 80% in Southeast Asia

- **Hb E carriers clinically silent, may have low MCV**

Hemoglobin E disorders

Condition	Genotype	Hb EP	Clinical features
Hb E trait	β^A/β^E	HbE 30%	Normal or low MCV
Hb E disease	β^E/β^E	HbE 90%	**Mild** microcytic anemia
Hb E/β thal **(Very common in SE Asia)**	β^E/β^0 or β^E/β^+	HbE 40-85%, **HbF 10-60%**	**Moderate to severe** microcytic anemia, ineffective erythropoiesis, iron overload
Hb SE disease	β^S/β^E	HBE 30% HbS 65%	**Mild sickling disorder**, like HbS/β^+ thalassemia

Hb EP – hemoglobin electrophoresis

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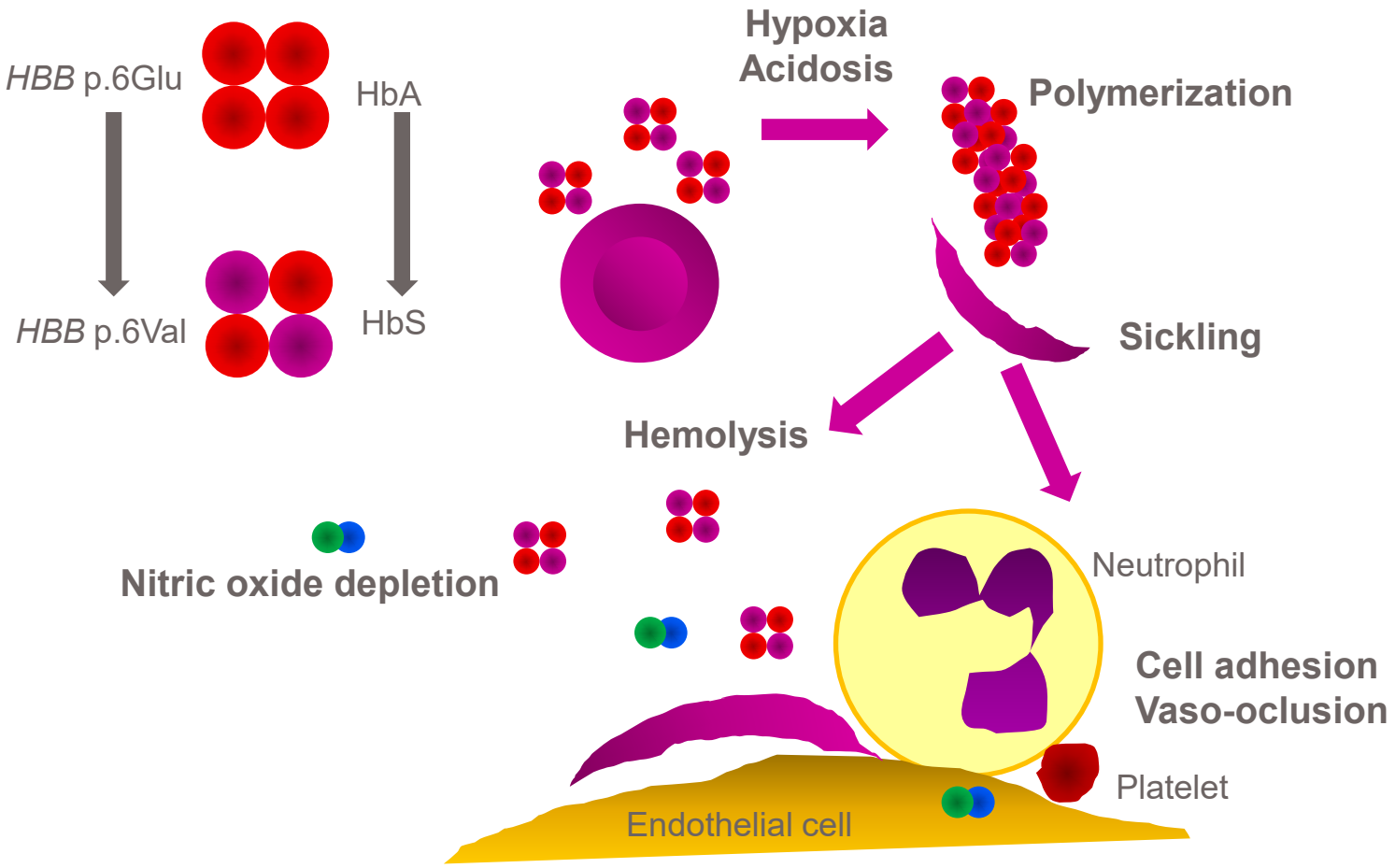
- Educational resources

Pathophysiology of sickle cell disease (SCD)



Question

A healthy African immigrant woman with sickle cell trait brings her 19- and 21-year-old sons by the same father for evaluation. Neither son has ever had a blood transfusion. You find on hemoglobin HPLC that the younger son has a report of $ASFA_2$ and the older $SAFA_2$.

You suspect:

A. Both sons have sickle cell trait
B. One son has sickle cell trait and the other has sickle cell anemia with α-thalassemia
C. One has sickle cell trait and the other has sickle-β-thalassemia
D. Lab error in reporting S and A out of order for in the older son
E. Incongruent paternity

Sickling syndromes

Table 1. Genotypes of Sickling Syndromes and Their Relative Severities

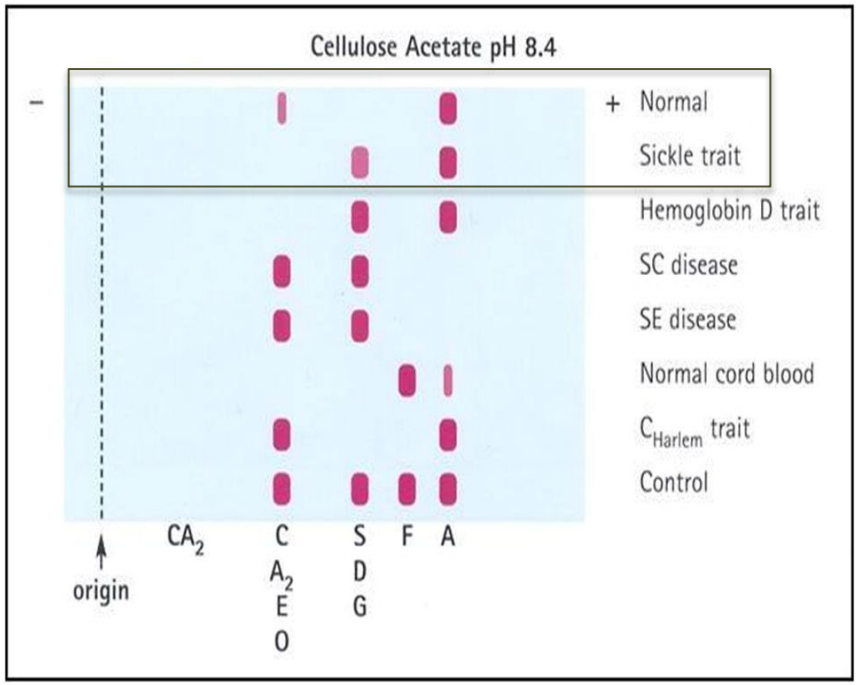
Genotype	Severity	Characteristics
HbSS	Severe	Most common form
HbSβ^0	Severe	Clinically indistinguishable from HbSS[6]
HbSO-Arab	Severe	Relatively rare[6]
HbSD-Punjab	Severe	Mostly in northern India[6]
HbSC-Harlem	Severe	Migrates like HbSC, but rare double β-globin mutation[7]
HbCS-Antilles	Severe	Rare double β-globin mutation[8]
HbSC	Moderate	25% of SCD[9]
HbSβ+, Mediterranean	Moderate	5%–16% HbA[6]
HbAS-Oman	Moderate	Dominant rare double β-globin mutation[10]
HbSβ+, African	Mild	16%–30% HbA[6]
HbSE	Mild	HbE found mostly in Southeast Asia[11]
HbS-HPFH	Very mild	Large deletions in β-globin gene complex; > 30% HbF[6]

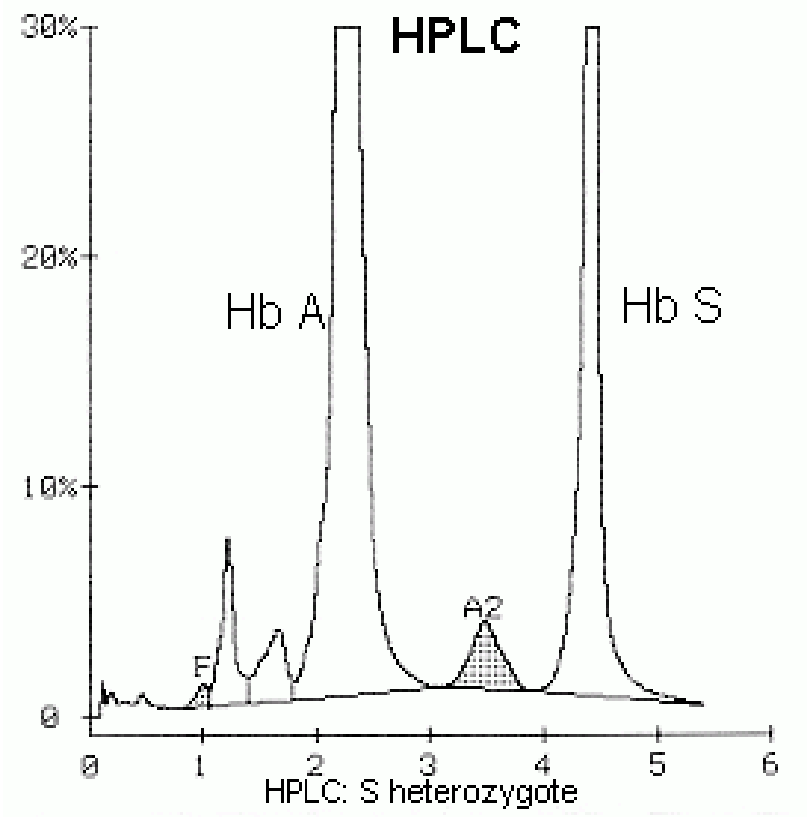
HbA = hemoglobin A; HbE = hemoglobin E; HbF = fetal hemoglobin; HbS-HPFH = HbS and gene deletion HPFH; HbSC = heterozygous hemoglobin SC; HbSS = homozygous hemoglobin SS; HbSβ^0 = hemoglobin S-β thalassemia^0; HbSβ+ = hemoglobin S-β thalassemia+; SCD = sickle cell disease.

Vivien A. Sheehan. Hematology-Oncology 12:1, 2-15

Laboratory diagnosis

- **Hemoglobin electrophoresis**
  - cellulose acetate (alkaline)
  - citrate agar (acidic)
- **High performance liquid chromatography (HPLC)**
  - currently most common test
- **Molecular biology**
  - PCR, gene sequencing





Sickle cell trait –evidence-based complications

- **High-quality, positive association**
  - Renal: Proteinuria, chronic kidney disease (CKD)
  - Vascular: venous thromboembolism (VTE), pulmonary emboli (PE)

- **Low-quality, variable association**
  - Exertion-related: sudden death
  - Renal: hematuria, end-stage renal disease (ESRD)
  - Vascular: HTN, MI, retinopathy, diabetic vasculopathy
  - Pediatric: sudden infant death syndrome (SIDS)
  - Surgery ± trauma-related: complications, length of stay
  - Overall mortality

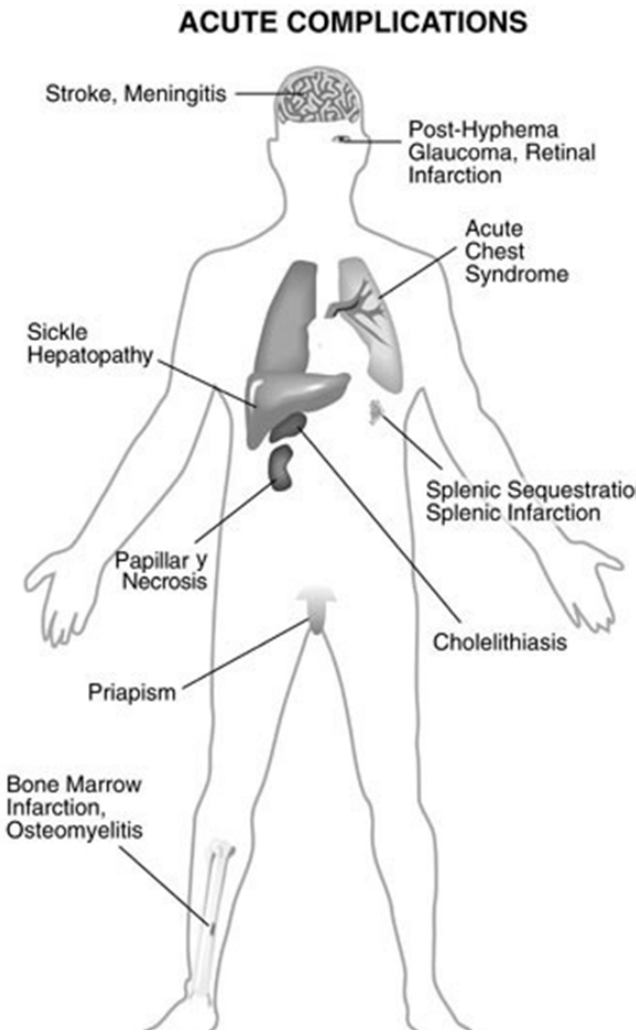
- **No evidence**
  - Exertion-related: splenic infarction
  - Renal: papillary necrosis, renal medullary cell carcinoma

Naik et al. *Ann Intern Med.* 2018 November 06; 169(9): 619-627. doi:10.7326/M18-1161

Hemoglobin SC disease – clinical manifestations

- Hemolytic anemia or compensated hemolytic state
- Sickled cells and HbC crystals
- Milder disease; 30% may have frequent pain episodes
- Splenomegaly frequent – may have mild thrombocytopenia due to hypersplenism
- Higher incidence of **avascular necrosis and retinopathy**

Clinical complications of SCD

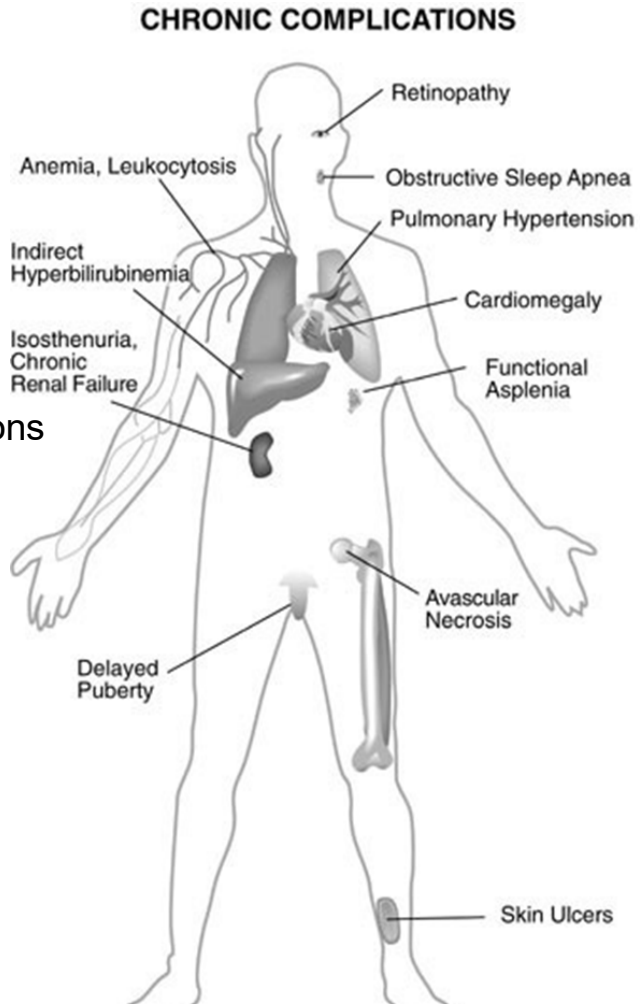


Acute complications

- Vasoocclusion (pain)
- Acute chest syndrome
- Acute stroke
- Priapism
- Hepatobiliary complications
- Splenic sequestration
- Acute renal failure

Chronic complications

- Pulmonary hypertension
- Ophthalmologic complications
- Avascular necrosis
- Leg ulcers
- Recurrent or stuttering priapism



Question

A 22-yo F with history of sickle cell anemia (HbSS) presents to the ED with severe chest pain and shortness of breath. She has copious sputum production, severe pain and low-grade fever. CXR reveals a RLL infiltrate. She is also hypoxic. She is started on broad spectrum antibiotics, IVF and a morphine PCA. She receives 2 units of packed RBCs. Despite these interventions, she remains in respiratory distress.

What additional therapy should be initiated at this time?

A. BiPAP

B. Albuterol

C. Hydroxyurea

D. RBC exchange

E. Sildenafil

Acute chest syndrome (ACS)

- Leading cause of death and 2nd most common cause of admissions in adults with SCD

- Suspect ACS when patients present with:
  - Fever ± hypoxia
  - Respiratory symptoms (dyspnea/cough/sputum)
  - New infiltrate on chest X-ray

- Triggers:
  - Infection (mostly children)
  - In-situ thrombosis
  - Fat emboli (more frequent in adults)

ST Miller. How I treat acute chest syndrome in children with sickle cell disease. Blood 2011; 117(20)

Acute care management in SCD

- Vaso-occlusive episodes (VOE)
  - Aggressive analgesia
  - Appropriate hydration
  - Check for triggers (infection, dehydration, acidosis)

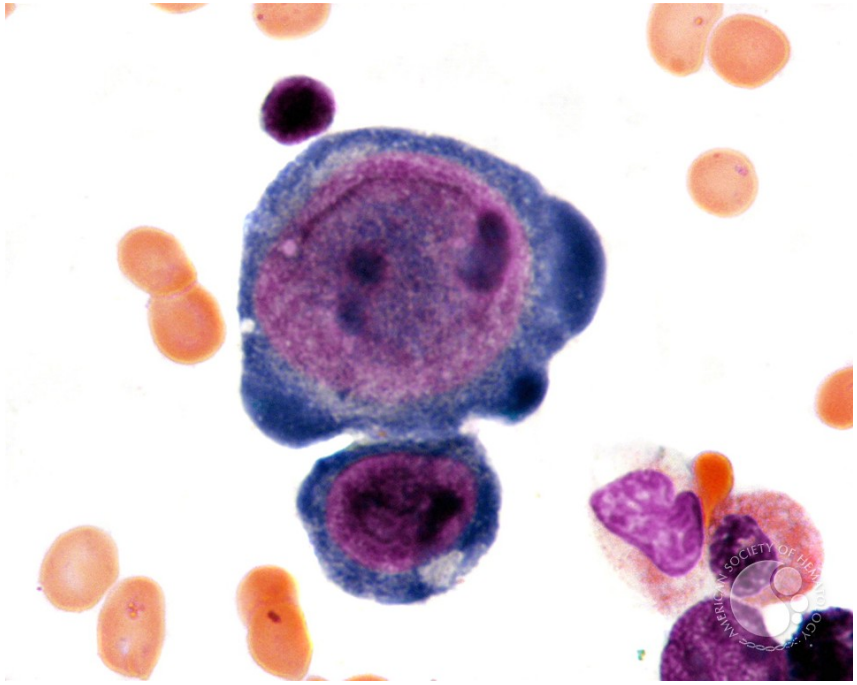
- Acute chest syndrome (ACS) → As above, also add
  - Empiric broad-spectrum antibiotics
  - Supplemental oxygen if SpO2<92%
  - Incentive spirometer, bronchodilators PRN
  - **Simple or exchange red cell transfusions**

- **DISCUSS STARTING HYDROXYUREA!**

ST Miller. How I treat acute chest syndrome in children with sickle cell disease. Blood 2011; 117(20)

Question

A 17 yo F with sickle cell anemia presents with profound fatigue and weakness. Her labs show Hb 4.3 g/dl (baseline 7.5 g/dl), MCV 84fL, and retic 1%. Her bone marrow core biopsy shows:



What is the most likely etiology of her severe anemia?

A. Splenic sequestration
B. Hyperhemolysis syndrome
C. Iron deficiency
D. Parvovirus infection
E. Folate deficiency

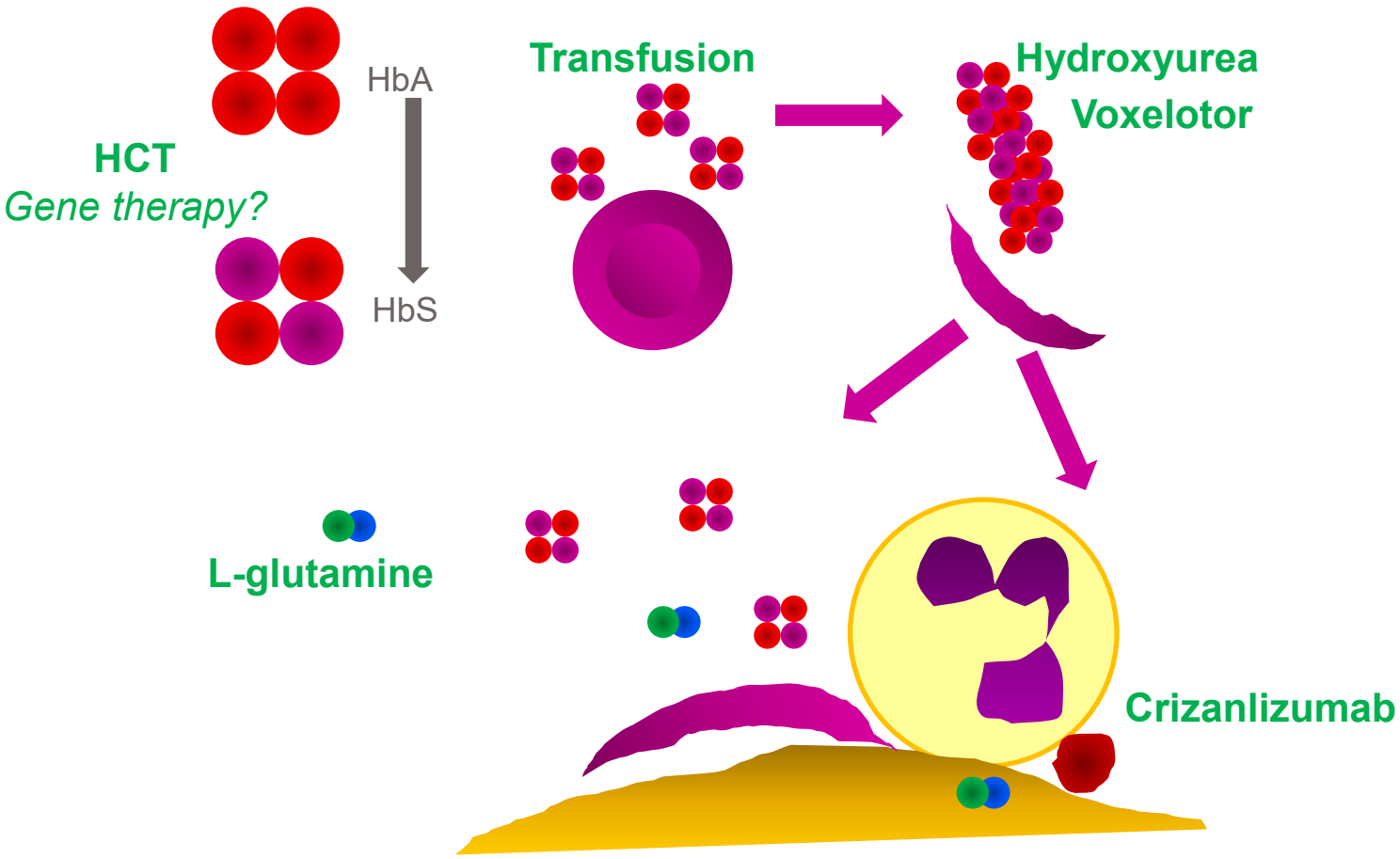
Aplastic crisis

- Cause: Parvovirus B19 infection
- May happen in ANY chronic hemolytic anemia
- Diagnosis:
  - Anemia with **reticulocytopenia**
  - Marrow: giant **proerythroblasts** with viral inclusions
  - **PCR+ for parvovirus** (serology is not useful)
- Management:
  - RBC transfusions, but avoid Hb overcorrection

ST Miller. How I treat acute chest syndrome in children with sickle cell disease. Blood 2011; 117(20)

Treatment of sickle cell disease (SCD)

Children < 5yrs: penicillin; adults and peds: folate supplementation



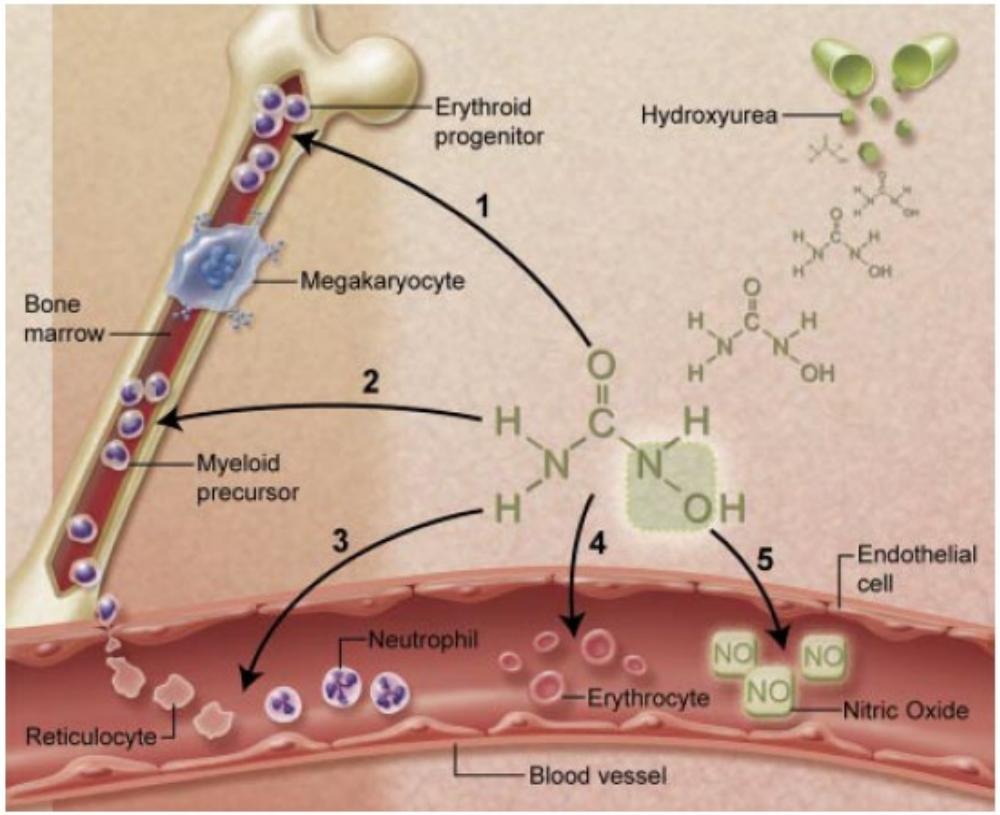
Hydroxyurea (HU)

Mechanisms of action:

1. HbF induction
2. Lower WBC, plts, retics
3. Decrease adhesion
4. Reduce hemolysis, improve RBC hydration, increase MCV
5. Nitric oxide donor

Decreases:

- Mortality
- Frequency/severity of VOEs
- Frequency of ACS
- Red cell transfusion



Russell E. Ware. *Blood* 2010 115:5300-5311;

Dose: HU 15-35mg/kg/day, titrate to maximum tolerated dose (target ANC ~ 2000)

Charache et a. *N Engl J Med.* 1995;332(20):1317-1322

When should you consider hydroxyurea?

Table 4. Indications for Hydroxyurea in Adult Patients with Sickle Cell Disease

Indication	Strength of Recommendation
SCA with ≥ 3 pain crises per year	Strong
SCA with pain that interferes with ADL and QoL	Strong
History of severe or recurrent ACS	Strong
Chronic kidney disease on epoetin	Weak
HbSβ+ and HbSC with pain that interferes with ADL and QoL; consult sickle cell disease expert	Moderate

ACS = acute chest syndrome; ADL = activities of daily living; QoL = quality of life; SCA = sickle cell anemia.

Vivien A. Sheehan. Hematology-Oncology 12:1, 2-15

Question

A 16-yo F with sickle cell anemia (HbSS) is admitted to the hospital for an acute ischemic stroke. Her baseline hemoglobin is 9 g/dL (Hb S 85-90%). What should be recommended to prevent further cerebral ischemia?

A. Simple transfusion to Hb>10g/dL

B. Simple transfusion to Hb>10g/dL and heparin drip

C. Red cell exchange transfusion to Hb>10g/dL

D. Red cell exchange transfusion to HbS<30%

E. Red cell exchange transfusion to HbS<20%

Question

She receives the RBC exchange transfusion and makes a full neurologic recovery from her acute cerebrovascular infarct.

Which of the following interventions should be recommended upon discharge?

A. Continue red cell exchange

B. Initiate hydroxyurea

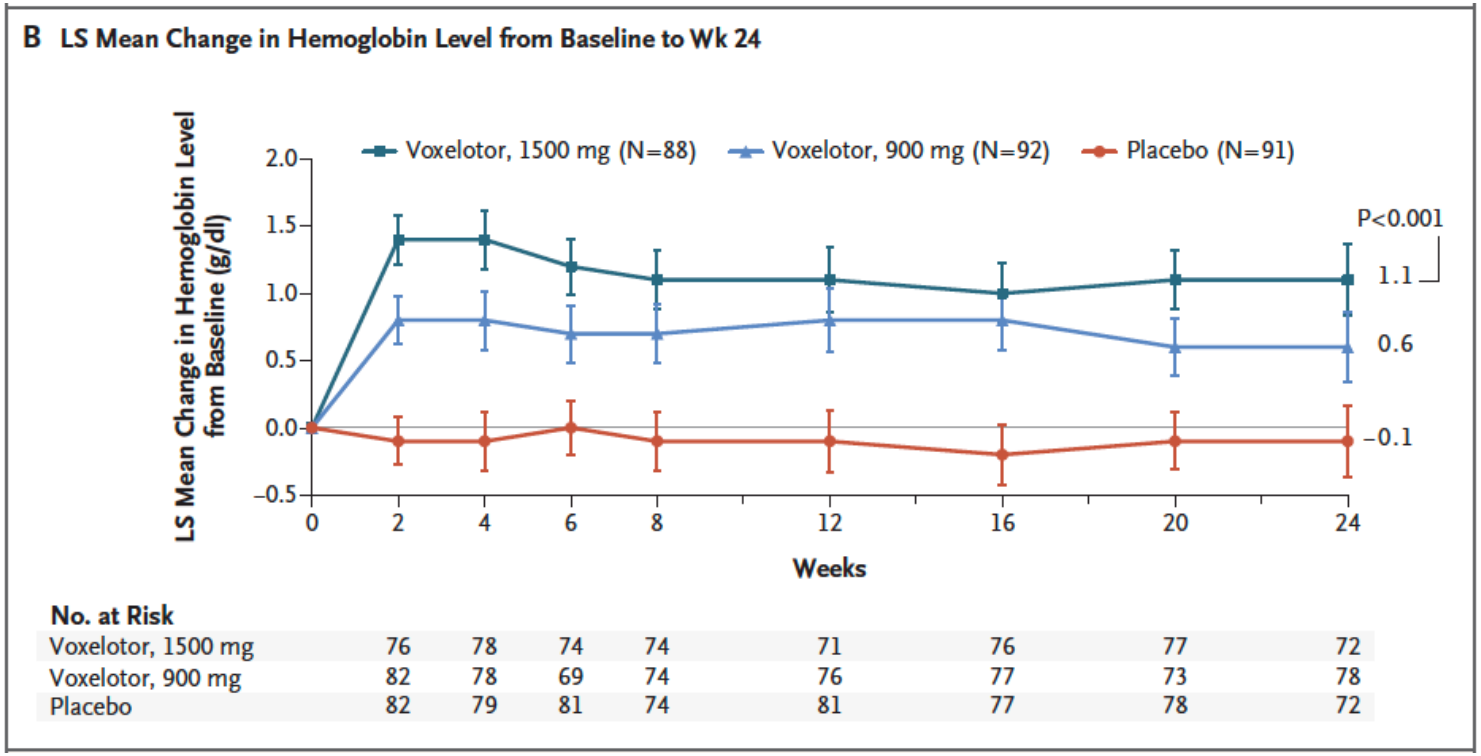
C. High dose folic acid (5 mg daily)

D. Simple transfusion to keep Hb>10g/dL

E. Erythropoietin to keep Hb > 10 g/dL

Novel agent to improve anemia in SCD

- **Voxelotor (Oxbryta®, previously GBT440)**
  - small molecule that stabilizes R state binding to amino-terminus of alpha chain of Hb
  - FDA-approved for SCD patients ≥ 12 years



Vichinsky E, Hoppe CC, Ataga KI, et al. *N Engl J Med.* 2019;381(6):509-519

Novel agents to decrease VOEs in SCD

- **L-glutamine (Endari®)**
  - Increases NADH and improves anti-oxidative defense
  - No change in Hb or hemolysis
  - Decrease in VOE frequency

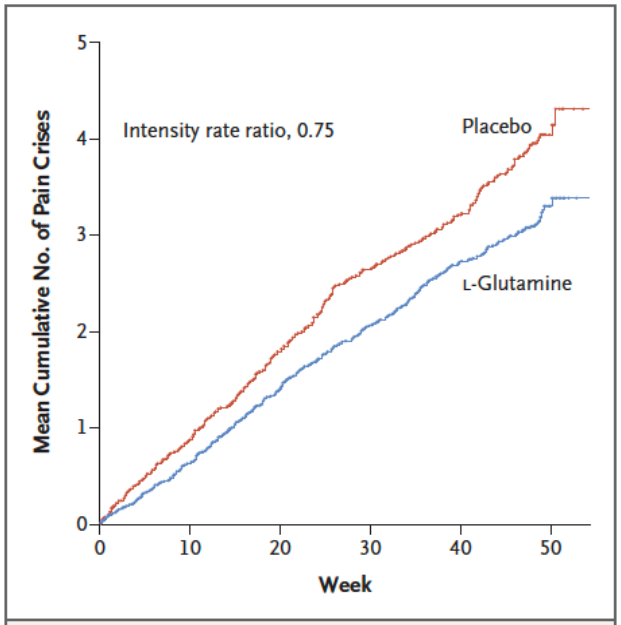


Figure 1. Recurrent Events of Sickle Cell–Related Pain Crisis over Time, According to Trial Group.

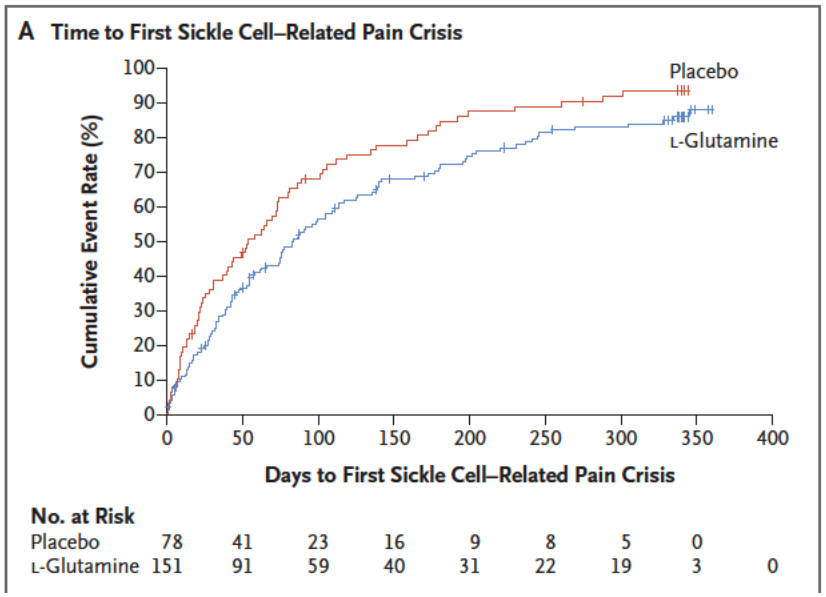
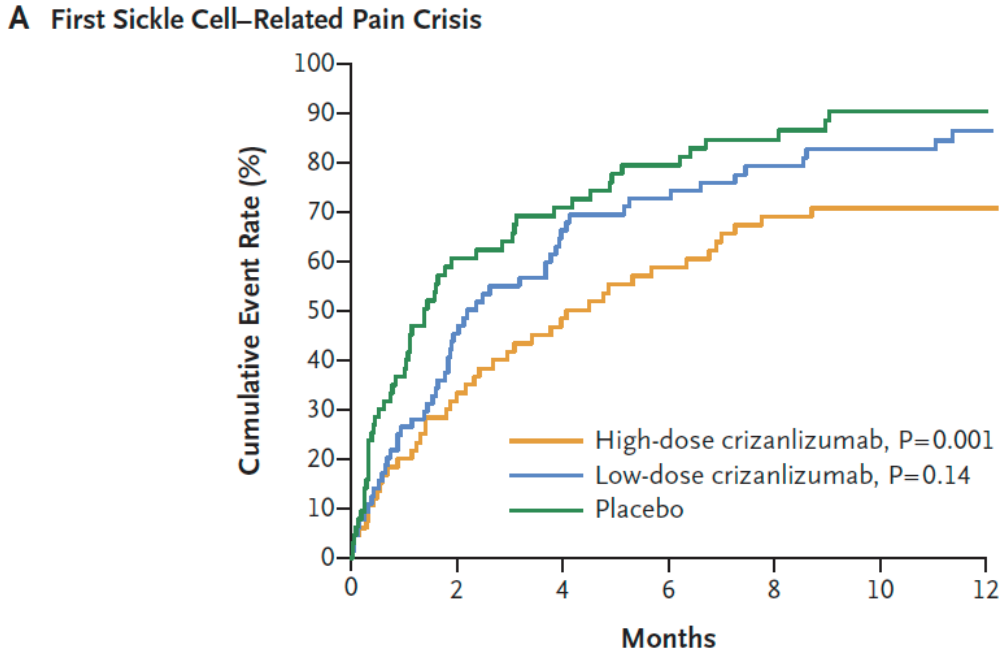


Figure 2. Time to Sickle Cell–Related Pain Crisis.

Niihara et al. N Engl J Med 2018 Jul 19;379(3):226-235.

Novel agents to decrease VOEs in SCD

- **Crizanlizumab (Adakveo®, previously SelG1)**
  - Humanized monoclonal anti-P-selectin antibody that reduces cell adhesion



Median Time to 1st pain crisis

High-Dose	4.1 months
Low-Dose	2.2 months
Placebo	1.4 months

Ataga KI et al. *N Engl J Med.* 2017;376(5):429-439

Question

A 32-yo male with sickle cell anemia (HbSS) is diagnosed with acute cholecystitis. He has not been compliant with his daily folic acid and hydroxyurea. He is slated for a cholecystectomy under general anesthesia. The surgery is considered medium risk. CBC reveals he is at his baseline hemoglobin level of 8.2 g/dL.

Which of the following should be done preoperatively?

A. Simple RBC transfusion
B. Folic acid
C. Hydroxyurea
D. Enoxaparin
E. RBC exchange transfusion

Question

An 18-year-old woman with HbSS on chronic transfusion therapy for primary stroke prevention develops back pain and fever 6 days after a routine pRBC transfusion. Her pre-transfusion hemoglobin was 8.3 g/dL; current hemoglobin is 5.7 g/dL. Her electrophoresis shows HbA 40%, HbS 60%, HbF 5%, and HbA_2 5%. Direct antiglobulin test (DAT) and indirect antiglobulin test (IAT) are negative; LDH level is elevated at 1205 U/L. Absolute reticulocyte count (ARC) is high at 450,000/µL.

What is the most likely diagnosis?

a. Aplastic crisis
b. New alloantibodies
c. Delayed hemolytic transfusion reaction (DHTR)
d. Hyperhemolysis syndrome
e. Splenic sequestration

Hyperhemolysis syndrome

- Severe complication of delayed hemolytic transfusion reaction
  - ➢ “Bystander hemolysis” of self-RBCs
- Most commonly diagnosed in people with SCD
- Post-transfusion Hb lower than pre-transfusion levels
- Increased hemolysis markers
- Management: immunosuppression, transfuse matched blood if unstable.

Adkins et al. *Transfusion and Apheresis Science.* 59 (2020) 102681

Curative therapies for SCD

- Allogeneic hematopoietic stem cell transplant

- *Gene therapy - investigational*
  - Gene addition e.g., anti-sickling Hb (HbA^{T87Q})
  - Gene editing (zinc-finger nucleases, CRISPR-Cas9) e.g., disruption of BCL11A
  - Gene editing and addition
  - Base pair editing

Ribeil et al. N Engl J Med 2017;376:848-55

ABIM Hematology exam blueprint

- **Thalassemias**
  - β-thalassemia
  - α-thalassemia
  - Hemoglobin E disorders

- **Sickle cell disorders**
  - Sickle cell trait
  - Sickle cell anemia (hemoglobin SS disease)
  - Hemoglobin SC disease and C hemoglobinopathy
  - Sickle cell-β^0 and sickle cell-β^+ thalassemias

- **Non-sickle hemoglobinopathies**

- **Educational resources**

Hemoglobin Lepore

- **Fusion** of β and δ globin genes
- Decreased synthesis of β-like globins
- **Homozygote: β-thal major phenotype**
  - 8-30% Hb Lepore
  - 70-92% Hb F
- Heterozygote: β-thal minor (trait) phenotype

Hemoglobin Constant Spring

- Non-deletional form of α-thalassemia
- Mutation in stop codon of α_2-globin adds 31 additional amino acids → 1% normal α-globin
- Homozygotes: more severe Hb H disease, but ~normal MCV

Hereditary persistence of HbF (HPFH)

- Clinically silent (e.g., found in blood donation)
- Up-regulation of γ chain synthesis
- Caused by:
  - deletions involving β and δ genes (nearly 100% HbF);
  - point mutations in γ chain promoter (variable HbF);
  - decreased expression of *KLF1*, transcription factor that activates fetal hemoglobin suppressor gene *BCL11A*
- Significantly modifies clinical outcomes when co-inherited with Hb S

Sickling syndromes

Table 1. Genotypes of Sickling Syndromes and Their Relative Severities

Genotype	Severity	Characteristics
HbSS	Severe	Most common form
HbSβ^0	Severe	Clinically indistinguishable from HbSS[6]
HbSO-Arab	Severe	Relatively rare[6]
HbSD-Punjab	Severe	Mostly in northern India[6]
HbSC-Harlem	Severe	Migrates like HbSC, but rare double β-globin mutation[7]
HbCS-Antilles	Severe	Rare double β-globin mutation[8]
HbSC	Moderate	25% of SCD[9]
HbSβ+, Mediterranean	Moderate	5%–16% HbA[6]
HbAS-Oman	Moderate	Dominant rare double β-globin mutation[10]
HbSβ+, African	Mild	16%–30% HbA[6]
HbSE	Mild	HbE found mostly in Southeast Asia[11]
HbS-HPFH	Very mild	Large deletions in β-globin gene complex; > 30% HbF[6]

HbA = hemoglobin A; HbE = hemoglobin E; HbF = fetal hemoglobin; HbS-HPFH = HbS and gene deletion HPFH; HbSC = heterozygous hemoglobin SC; HbSS = homozygous hemoglobin SS; HbSβ^0 = hemoglobin S-β thalassemia^0; HbSβ+ = hemoglobin S-β thalassemia+; SCD = sickle cell disease.

Vivien A. Sheehan. Hematology-Oncology 12:1, 2-15

Unstable hemoglobin disease

- Congenital chronic non-spherocytic anemia
  - variable severity
  - ± low MCV
- Rare, AD mutations →defective heme binding by globin chains
- Diagnosis:
  - Heinz bodies precipitation in RBCs on isopropanol test
  - About 200 “unstable” Hb variants → DNA sequencing
- Hb Köln most common: anemia, retics (10-25%), splenomegaly
- Treatment: avoid oxidant drugs, RBC transfusions as needed, splenectomy

Hemoglobin M disorders

- **Hereditary methemoglobinemias:**
  - Asymptomatic cyanosis, slate grey/brownish skin, no dyspnea or hypoxia
  - Autosomal dominant (AD)
  - Amino acid substitution in heme pocket: $Fe^{2+} \rightarrow Fe^{3+}$, cyanosis

- **Diagnosis:** abnormal SpO2, Hb electrophoresis or spectra, **methemoglobin < 30%**

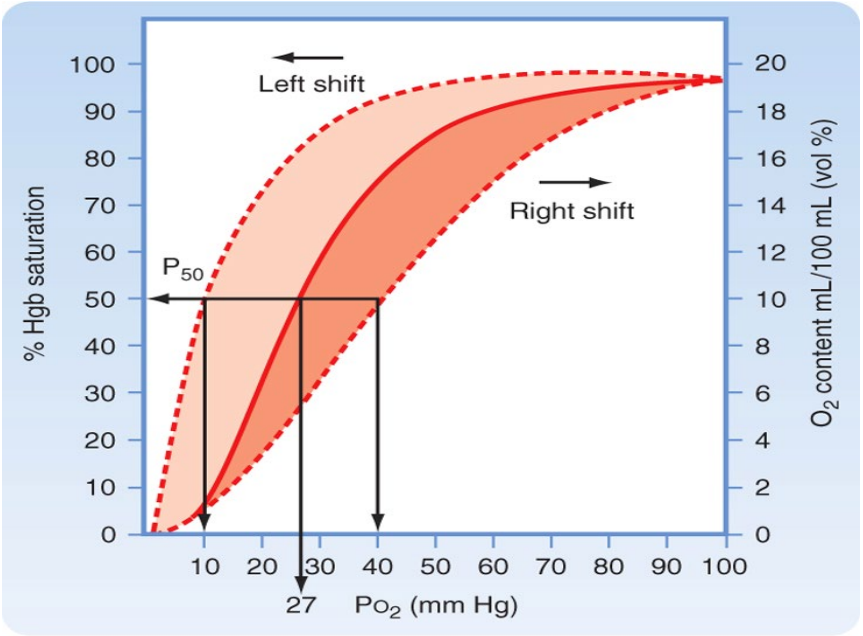
- No treatment needed, cyanosis ***not*** reversible with methylene blue or vitamin C

- Different from other methemoglobinemias (treat with methylene blue)

- **Toxins:** nitrites, sulfanilamide, dapsone, primaquine, etc.
  - Symptomatic with metHb> 30% (> 50% is lethal!)
- **Congenital deficiency in cytochrome b5 reductase:** $Fe^{3+} \rightarrow Fe^{2+}$
  - cyanosis improves with methylene blue or vitamin C

Other hemoglobin disorders

- **Hb with high O_2 affinity:**
  - AD, familial **erythrocytosis**,
  - α or β-chains can be affected
  - Diagnosis: low P_{50} (left shifted on O_2 dissociation curve), variant Hb in electrophoresis, DNA sequencing
  - No phlebotomy unless Ht >60%
  - Differential dx: polycythemia vera, secondary polycythemias



- **Hb with low O_2 affinity:**
  - Right shift on O_2 dissociation curve (high P_{50} ~ 30-40 mmHg)
  - Cyanosis, but otherwise asymptomatic (depending on degree of right shift)
  - No treatment required

Educational resources

- NHBLI Evidence-based Management of Sickle Cell Disease- Expert Panel Report (2014)

- Thalassemia International Foundation (TIF) publications www.thalassaemia.org.cy

- American Society of Hematology, ASH (www.hematology.org)
  - ASH Self-Assessment Program (ASH SAP), 7th Ed.
  - All Grown Up: Ensuring Effective Care Transition in β-Thalassemia Program
  - Benign Hematology Curriculum – Sickle Cell Disease

- ASH Pocket Guides (download from App store)

- Hematology/Oncology question bank hemeoncquestions.com/

Special thanks: Drs. Kleber Fertrin, Victor Gordeuk, Ravin Garg, and Vivien Sheehan

THANK YOU