Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Hemoglobin disorders

Kleber Y. Fertrin, MD, PhD

Assistant Professor, University of Washington

Director, Hemolytic Anemias and Iron Disorders Program

kleber@uw.edu

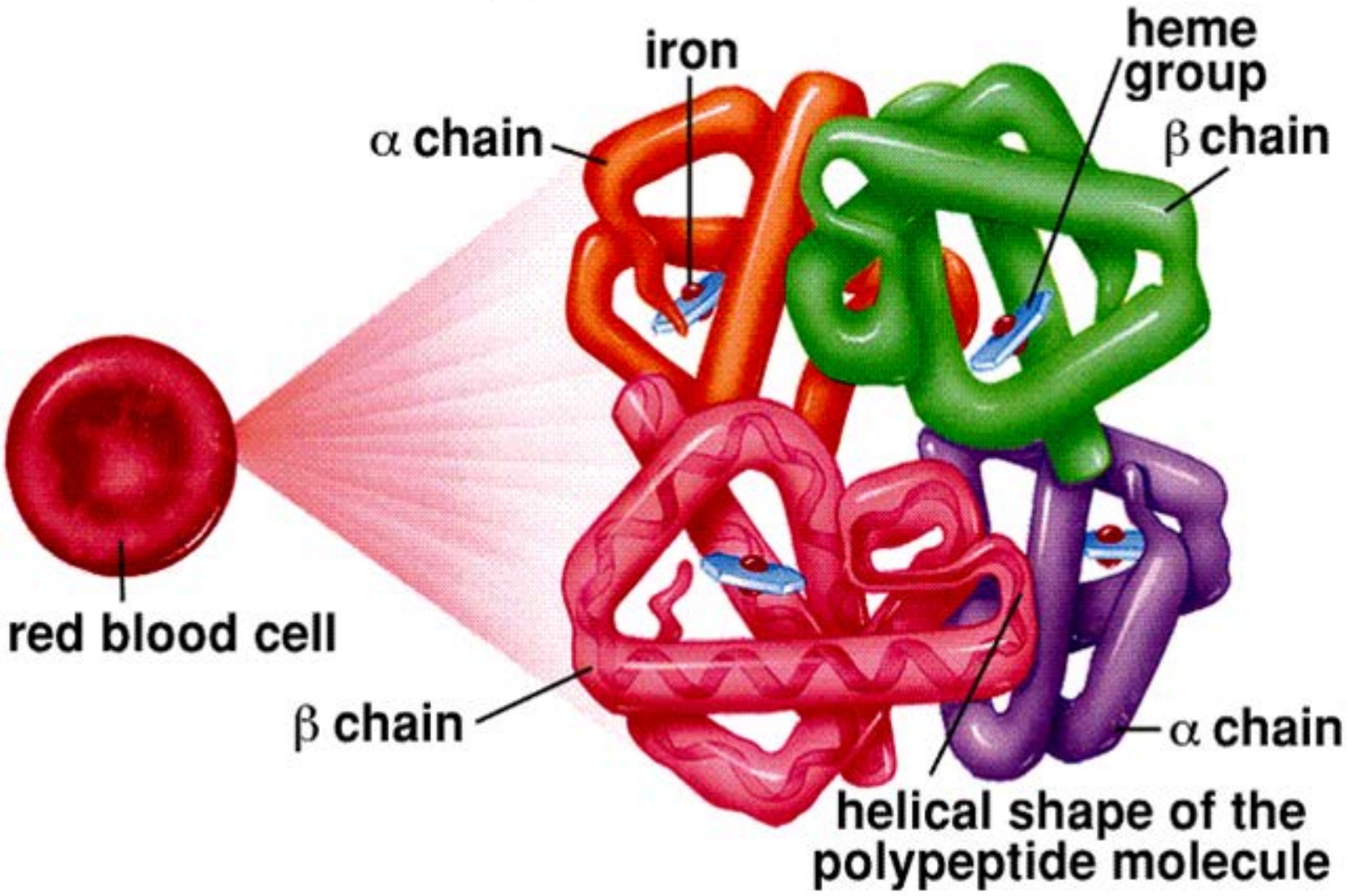
DISCLOSURES

Agios Pharmaceuticals – Research funding, Advisory Board

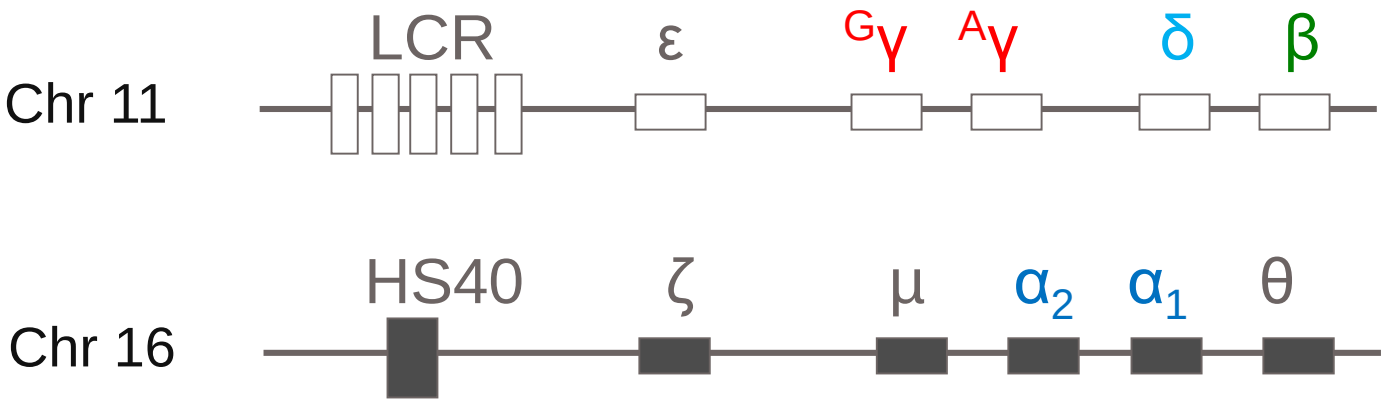
ABIM Hematology exam blueprint

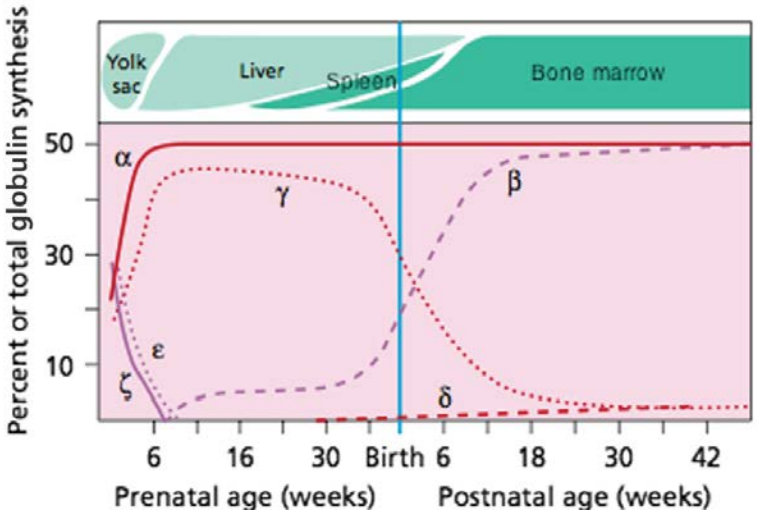
Red blood cell destruction disorders *(15% of exam)*						
Thalassemias						
Alpha thalassemia	LF	⊘	⊘	⊘	⊘	⊘
Beta thalassemia	LF	⊘	⊘	⊘	⊘	⊘
Hemoglobin E disorders	LF	⊘	⊘	⊗	⊗	⊗
Sickle cell disorders *(4.5% of exam)*						
Sickle cell trait		⊘	⊘	⊘	⊘	⊘
Sickle cell anemia (hemoglobin SS disease)		✓	✓	✓	✓	⊘
Hemoglobin SC disease	LF	⊘	⊘	⊘	⊘	⊘
Sickle cell-beta zero and sickle cell-beta plus-thalassemias	LF	⊘	⊘	⊘	⊘	⊘
Non-sickle hemoglobinopathies	LF	⊘	⊘	⊘	⊗	⊗

Hemoglobin Molecule



Globin genes and hemoglobins





Postembryonic hemoglobin species

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

Figure 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

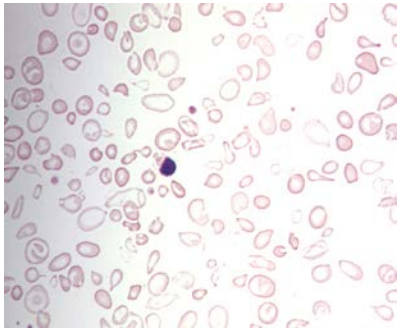
β^0 (null) = No gene product

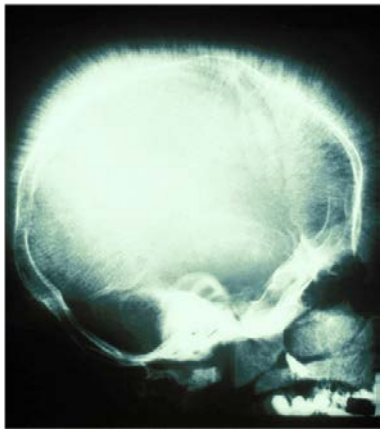
β^+ = reduced production

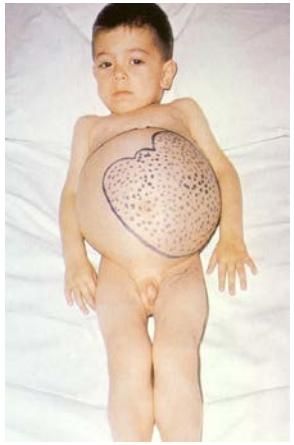
- **Excess α-globin chains → <u>INEFFECTIVE ERYTHROPOIESIS</u>**
  - α-globin aggregates in erythroid precursors → intramedullary death
- **Excess free intracellular iron:**
  - membrane lipid oxidation
  - membrane protein damage
- **Membrane damage → PS* exposure and hypercoagulability**
  - decreased RBC deformability
  - increased clearance from circulation

PS phosphatidylserine

Pathophysiology and 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)	Transf	Clinical features	Most common genotype
Thalassemia minor (trait)	**10-12**	**No**	No hemolysis or symptoms, **RBC>5million**, **HbA_2>3.5%**	**β^0/β or β^+/β**
Thalassemia intermedia	7-10	+/-	**high Hb F,** bone disease, **transfusion and/or spontaneous** iron overload, splenomegaly*, pulm HTN, leg ulcers	**β^+/β^+ or β^+/β^0**
Thalassemia major	<7	Age<2	**>95% HbF**, bone disease, **transfusion** iron overload, splenomegaly*	**β^0/β^0 or β^0/β^+**

*splenomegaly due to increased hemolysis, extramedullary hematopoiesis

β-thalassemia major: current treatment

Referral to comprehensive medical center

- Hematology, Genetics, Cardiology, Hepatology, Endocrinology, Ob/Gyn

Palliative care:

- **Transfusion:** typically 2-3 pRBCs q 3-4weeks
  - Goals:
    - 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)**

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: transfusion >200-220mL/kg/year; untransfusable 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 ppx

- **Luspatercept**
  - FDA-approved for TD beta thal in 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
  - AE: bone pain, headache, asthenia

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

β-thalassemia major: current treatment

Curative treatments:

- **Allogeneic hematopoietic cell transplantation**
  - Ideally: age<14; HLA-matched sibling donor; no significant iron overload.
    - **Pesaro system: predicts post-BMT 3-year OS in children<16yo**

      Adverse factors:

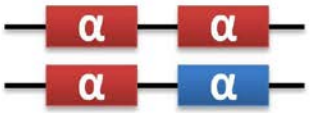
      1. Hepatomegaly >2cm from costal arch
      2. Liver fibrosis on biopsy
      3. Irregular iron chelation

      - Class I: 0 adverse factors → 94%
      - Class II: 1 or 2 adverse factors → 80%
      - Class III: all adverse factors → 61%

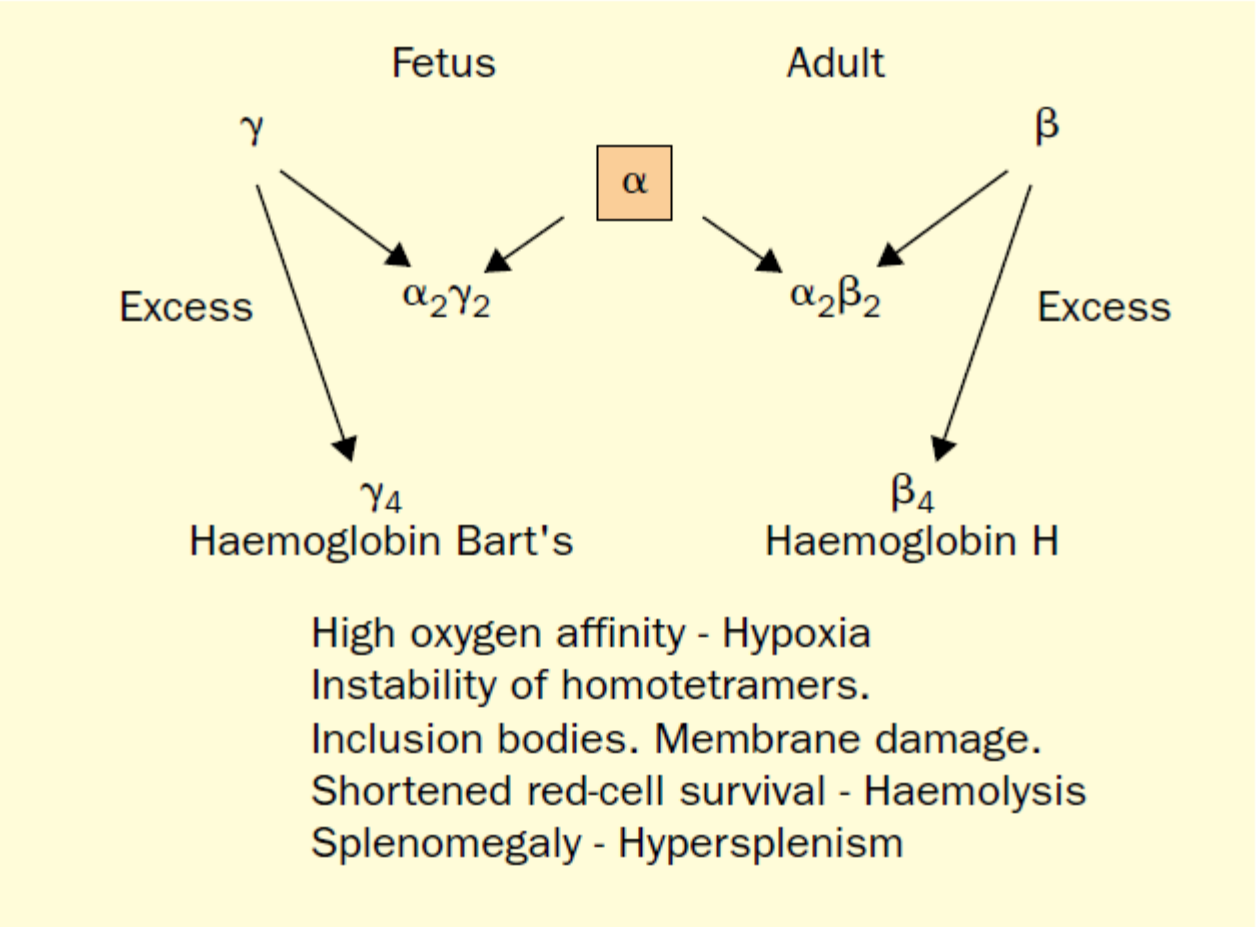
- *Investigational: LentiGlobin gene therapy*
  - Thompson et al. N Engl J Med. 2018 Apr 19;378(16):1479-1493

α thalassemia genetics

Chromosome 16

Normal		**Normal αα/αα**
Carrier: Asymptomatic WNL or isolated microcytosis		**α^+ trait: α-/αα**
α-thal minor: Asymptomatic Mild microcytic anemia	**homozyg α^+ trait** -α/-α  or **α^0 trait** --/αα 	
Hb H Disease: Symptomatic Hemolytic and Microcytic anemia Splenomegaly		**Hb H disease --/-α**
Incompatible with Life Hydrops Fetalis		**Hydrops fetalis --/--**

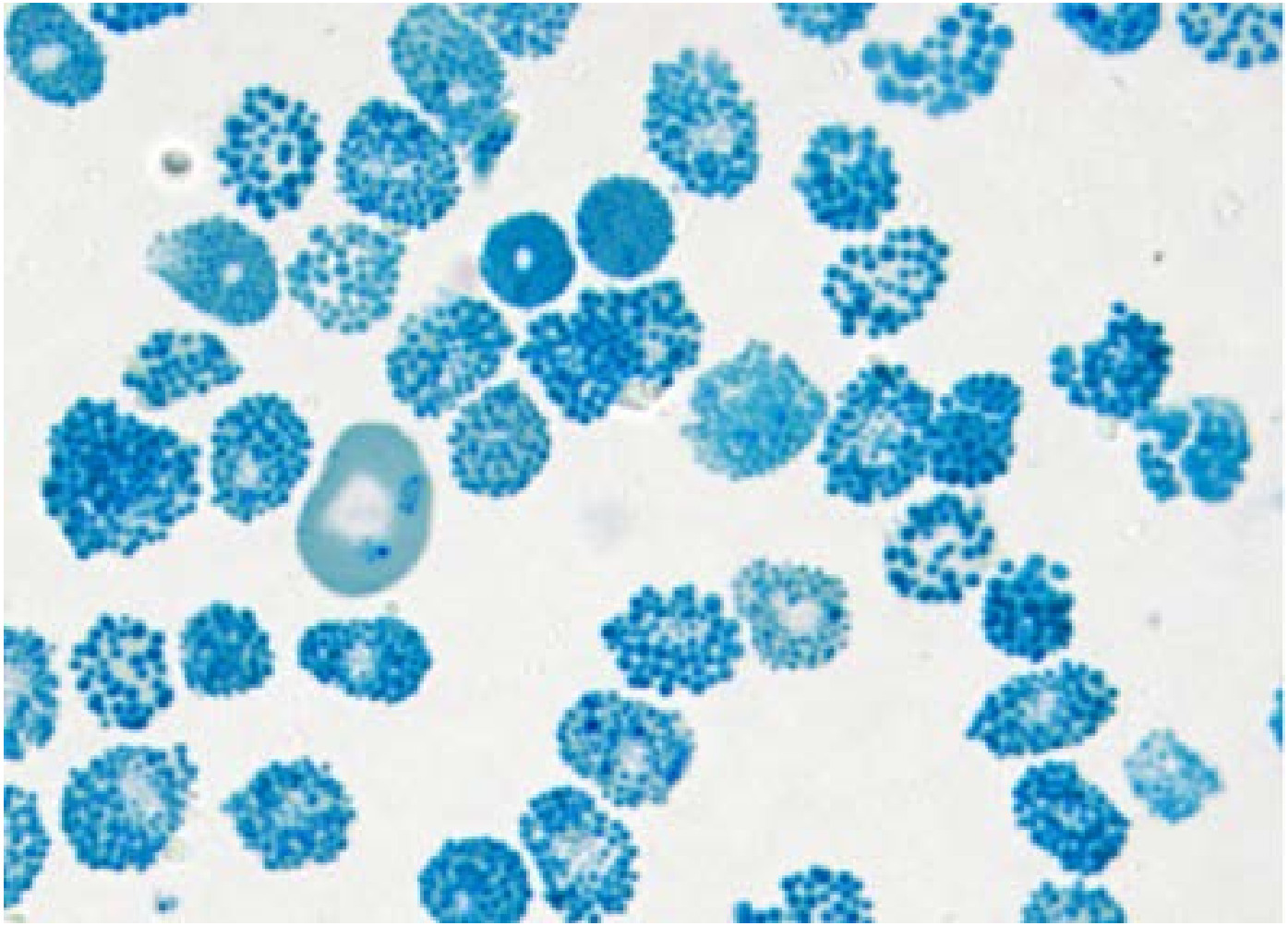
Pathophysiology of α-thalassemias



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

Weatherall and Proven. *Lancet* 2000;355:1169-1175

RBC inclusions in Hb H disease



Additional information on α thalassemia

- **If suspecting α thalassemia carrier state or trait:**
  - 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 α thalassemias:**

  <u>α thalassemia-intellectual disability syndromes</u>
  - ATR-16 syndrome : large deletions in α-globin genes on chromosome 16
  - ATR-X syndrome: mutations in ATRX gene (chromatin-associated protein)

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

Treatment for α thalassemias

- **Hb Bart's hydrops fetalis (--/--)**
  - Intrauterine transfusions followed by chronic transfusions and chelation
  - screening, genetic counseling in high risk populations
  - hematopoietic cell transplantation has been done

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

- **Milder α thalassemias (α-/α- or αα/--)**
  - genetic counseling
  - avoid unnecessary iron supplementation

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 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

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**, similar to HbS/β^+ thalassemia

ABIM Hematology exam blueprint

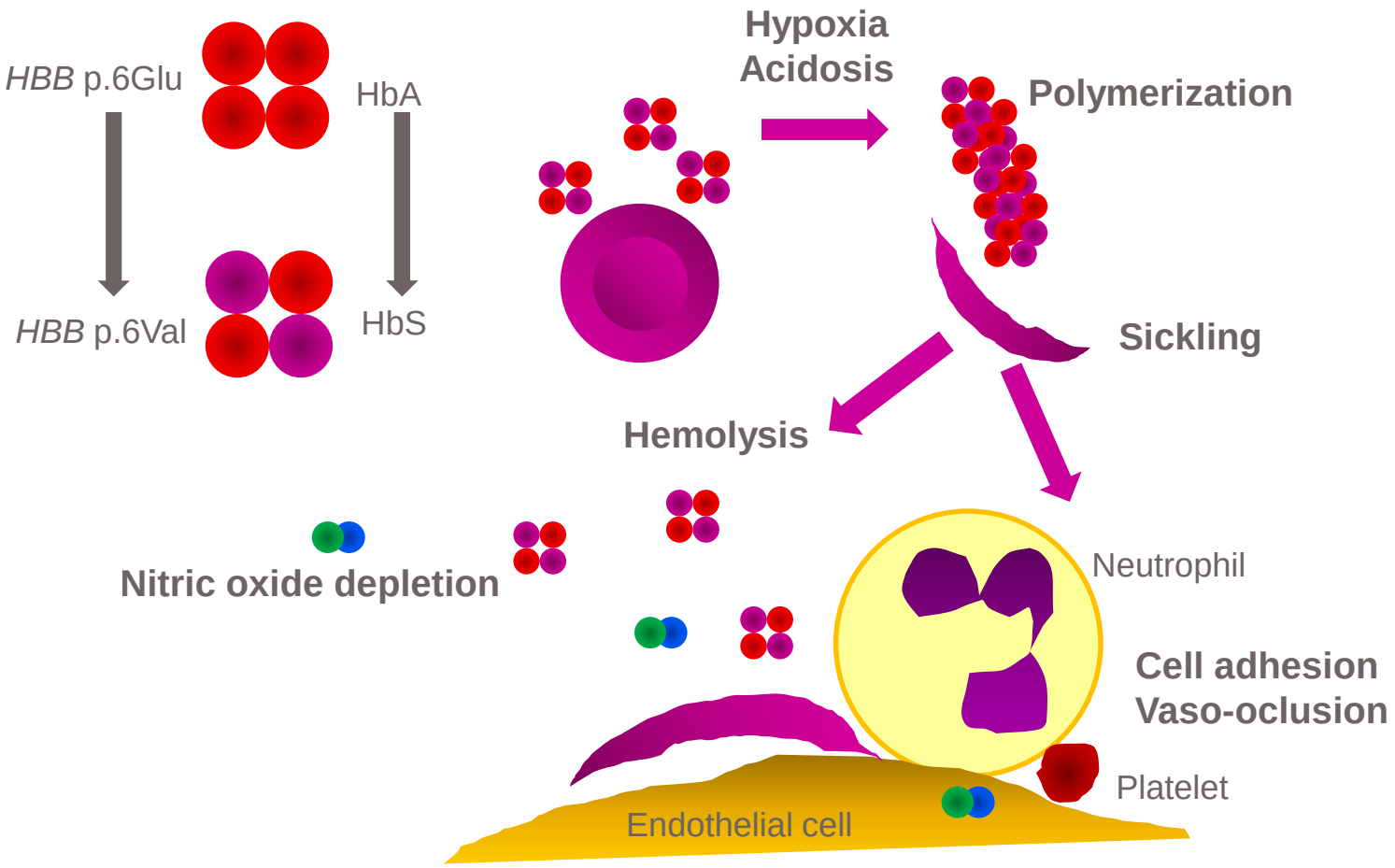
- Thalassemias
  - β-thalassemia
  - α-thalassemia
  - Hemoglobin E disorders

- **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

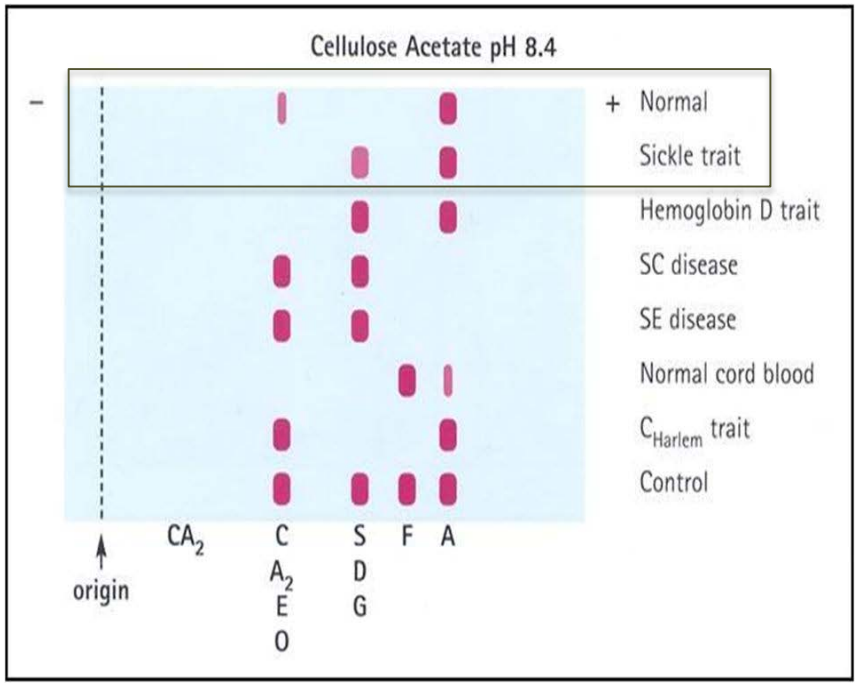
- Educational resources

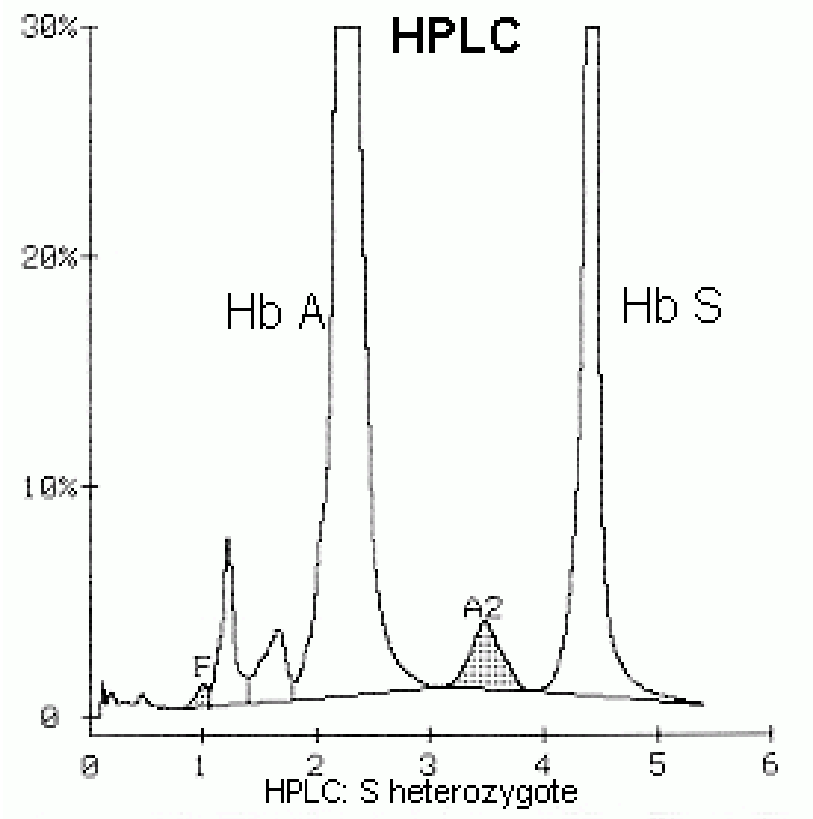
Pathophysiology of sickle cell disease (SCD)



Laboratory diagnosis

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





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

Sickle cell trait

- HbAS → 35-40% HbS and 55-60% HbA, no anemia

Clinical manifestations

- Renal disease:
  - Hematuria due to renal papillary necrosis
  - Hyposthenuria
  - CKD
  - UTI
  - Renal medullary carcinoma
- Splenic infarction or sequestration
  (high altitude / scuba diving / dehydration)
- Exertional sudden death / rhabdomyolysis
- Higher risk of PE (OR 3.9)
- Traumatic hyphema may lead to acute glaucoma

Tsaras et al. *Am J Med.* 2009;122(6):507-512.

Hemoglobin SC disease

Clinical manifestations

- CBC:
  - Hemolytic anemia or compensated hemolytic state
  - Sickled cells and HbC crystals

- Milder disease; 30% may have frequent VOC
- Splenomegaly frequent – may have mild thrombocytopenia due to hypersplenism
- Higher incidence of AVN and retinopathy

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 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

Sickle cell disease (SCD)

- Acute manifestations
  - Vaso-occlusive crisis
  - Acute chest syndrome
  - Stroke (isch/hemorrh)
  - Sequestration (hepatic/splenic)
  - Acute intrahepatic cholestasis
  - Aplastic crisis
  - Priapism

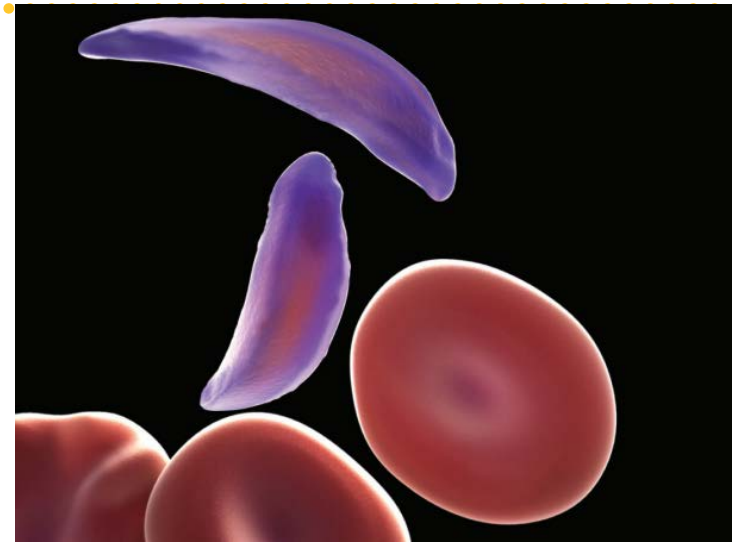


Image courtesy of National Institute of Health

Sickle cell disease (SCD)

- Chronic complications and end-organ damage
  - Retinopathy
  - Heart failure
  - Pulmonary hypertension
  - Gallstones
  - Hypersplenism/Asplenia
  - Avascular necrosis
  - Osteopenia/osteoporosis
  - CKD
  - Recurrent or stuttering priapism
  - Leg ulcers / osteomyelitis

Image courtesy of National Institute of Health

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 admission in adult SCD patients
- Diagnosis:
  - Fever,
  - Respiratory sx (dyspnea/cough/sputum)
  - New infiltrate on CXR
  - ±Hypoxia
- 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)

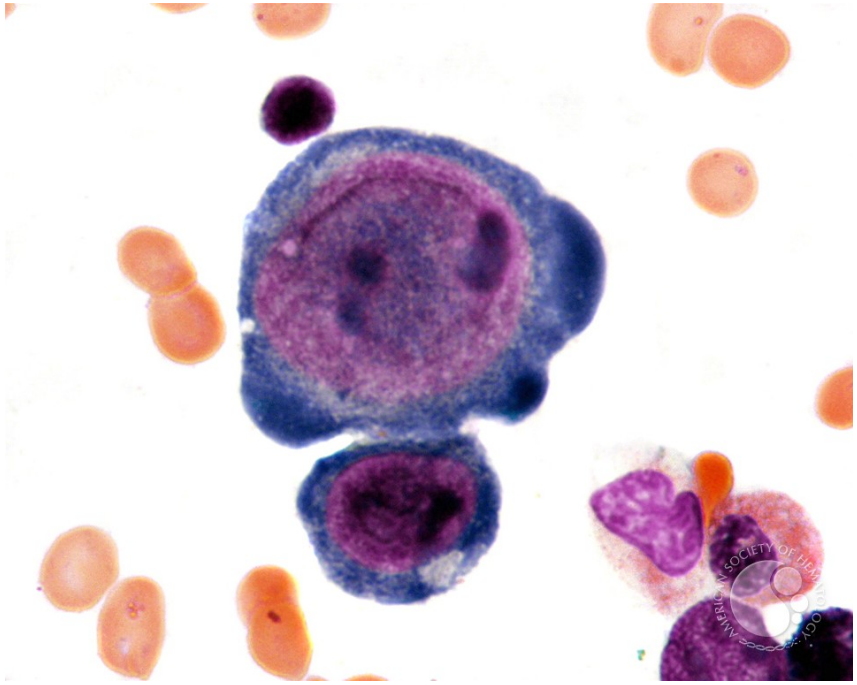
VOC and ACS management

- VOC:
  - Aggressive analgesia
  - Appropriate hydration
  - Check for triggers (infection, dehydration, acidosis)
- ACS → 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 cause of her severe anemia?

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

Aplastic crisis

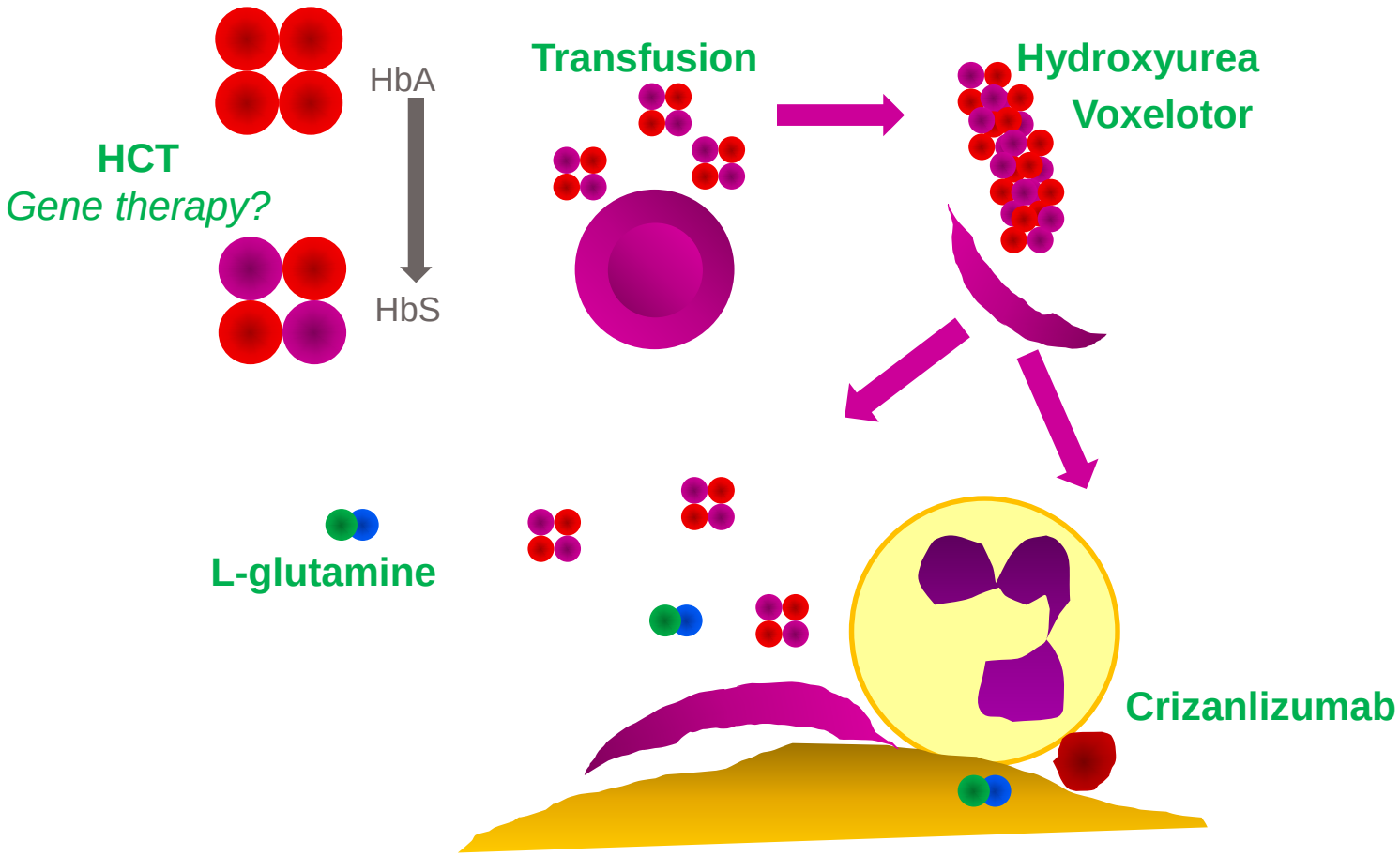
- Cause: parvovirus B19 infection
- May happen in ANY chronic hemolytic anemia
- Diagnosis:
  - Anemia with **reticulocytopenia**
  - Marrow: giant **proerythroblasts** with viral inclusions
  - **PCR+ for parvovirus** (serology is not useful)

- Management: transfusions for support; 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<5y: penicillin; All: folate supplementation



Hydroxyurea

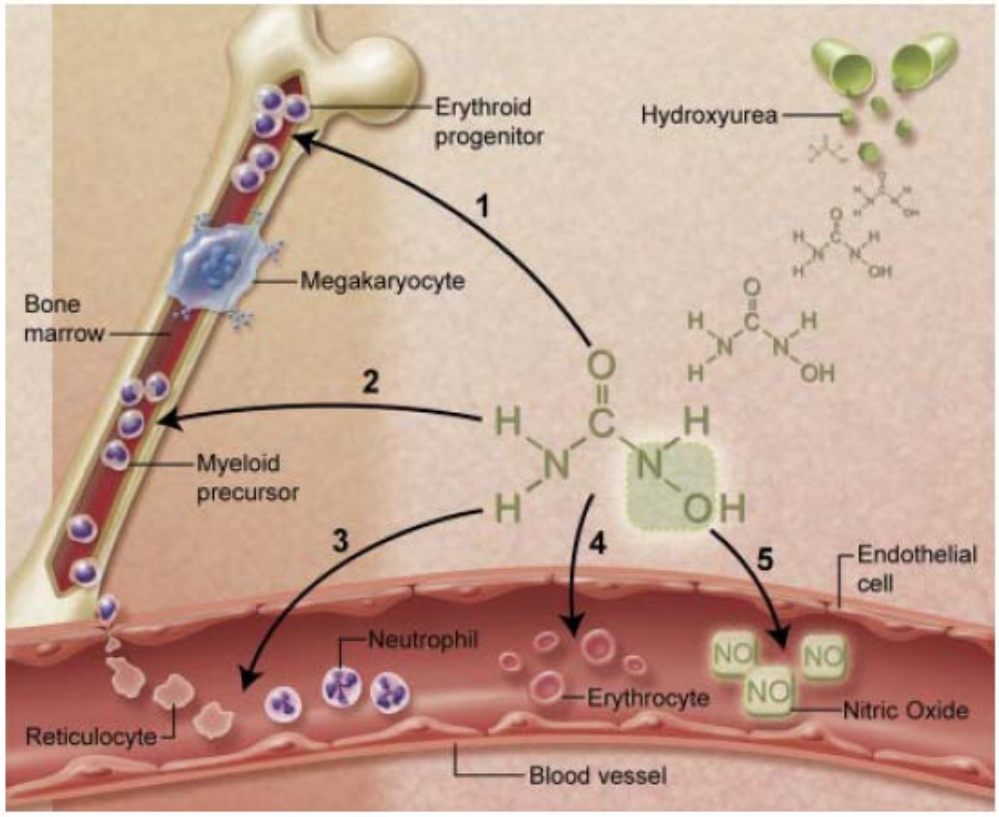
Mechanisms of action:

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

Decreases:

- Mortality
- Frequency of VOC
- Frequency of ACS
- Red cell transfusion

Dose: 15-35mg/kg/day



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

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

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. Simples transfusion to keep Hb>10g/dL

E. Erythropoietin to keep Hb > 10 g/dL

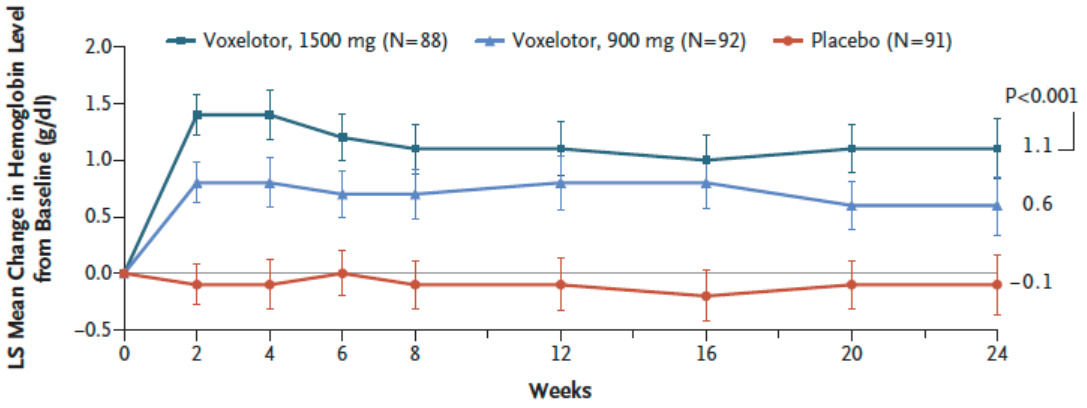
Novel agent to improve anemia in SCD

- Voxelotor (Oxbryta®, previously GBT440)

  Vichinsky et al. *N Engl J Med*. 2019 381(6):509-519. doi:10.1056/NEJMoa1903212

  - small molecule that stabilizes R state binding to amino-terminus of alpha chain of Hb

B **LS Mean Change in Hemoglobin Level from Baseline to Wk 24**



No. at Risk								
Voxelotor, 1500 mg	76	78	74	74	71	76	77	72
Voxelotor, 900 mg	82	78	69	74	76	77	73	78
Placebo	82	79	81	74	81	77	78	72

Novel agents to decrease VOC in SCD

L-glutamine (Endari®)

Niihara et al. N Engl J Med 379;3 July 19, 2018

- Increases NADH and improves anti-oxidative defense
- No change in Hb or hemolysis
- Decrease in VOC frequency

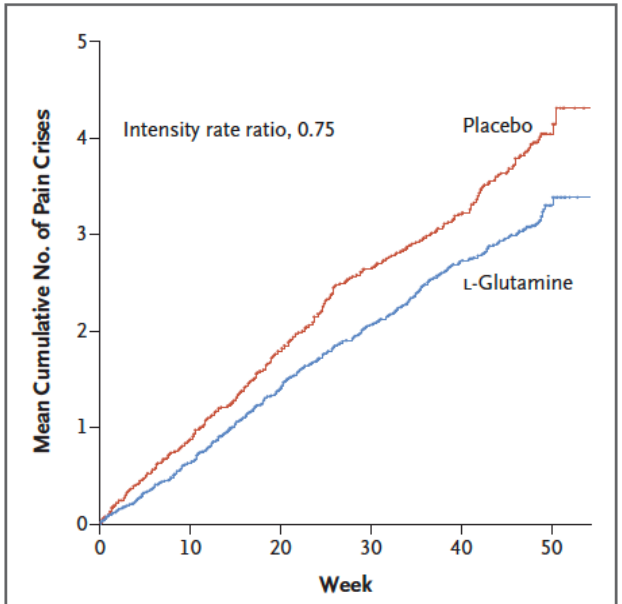


Figure 1. Recurrent Events of Sickle Cell–Related Pain Crisis over Time, According to Trial Group.

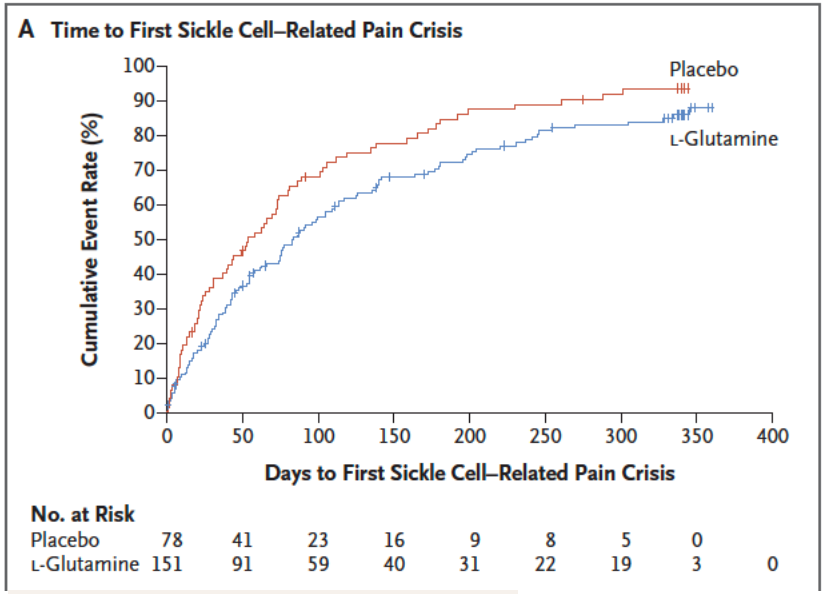


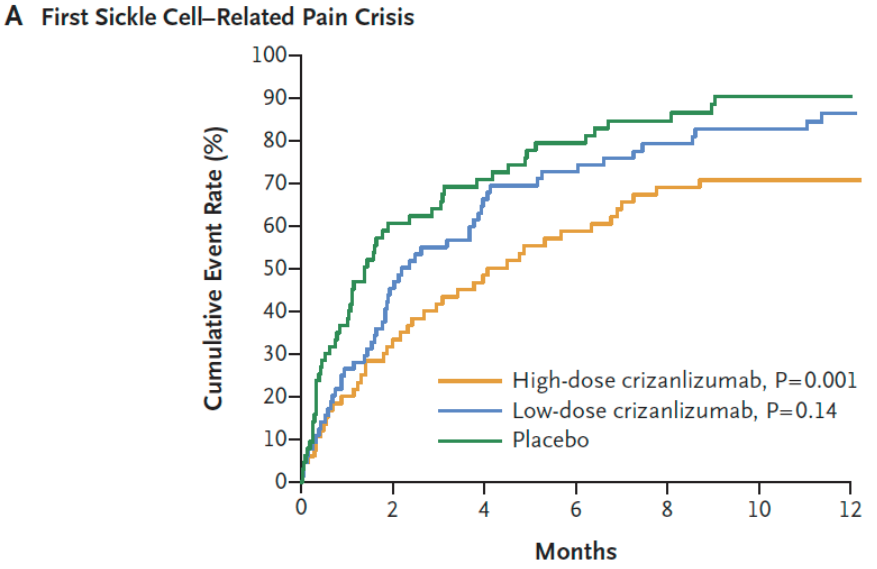
Figure 2. Time to Sickle Cell–Related Pain Crisis.

Novel agents to decrease VOC in SCD

Crizanlizumab (Adakveo®, previously SelG1)

Ataga et al. N Engl J Med 376;5 Feb 2, 2017

- Humanized monoclonal anti-P-selectin antibody that reduces cell adhesion



No. at Risk													
High-dose crizanlizumab	67	49	41	35	30	26	24	20	18	17	16	15	7
Low-dose crizanlizumab	66	47	34	28	21	19	17	15	12	10	10	10	3
Placebo	65	37	23	21	17	13	12	9	8	6	5	4	1

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. CBC shows 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 Hb was 8.3 g/dL; current Hb is 5.7 g/dL. Her electrophoresis shows HbA 40%, HbS 60%, HbF 5%, and HbA_2 5%. Direct antiglobulin test (DAT) and screen are negative; LDH level is elevated at 1200 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

Novel therapies for sickle cell disease

Gene therapy - investigational

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

- 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

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) pheno**type

Hemoglobin Constant Spring

- Non-deletional form of α-thalassemia
- Mutation in stop codon of α_2-globin adds 31 additional aminoacids → 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 HbF suppressor gene *BCL11A*

- Significantly modifies clinical outcomes when co-inherited with Hb S

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

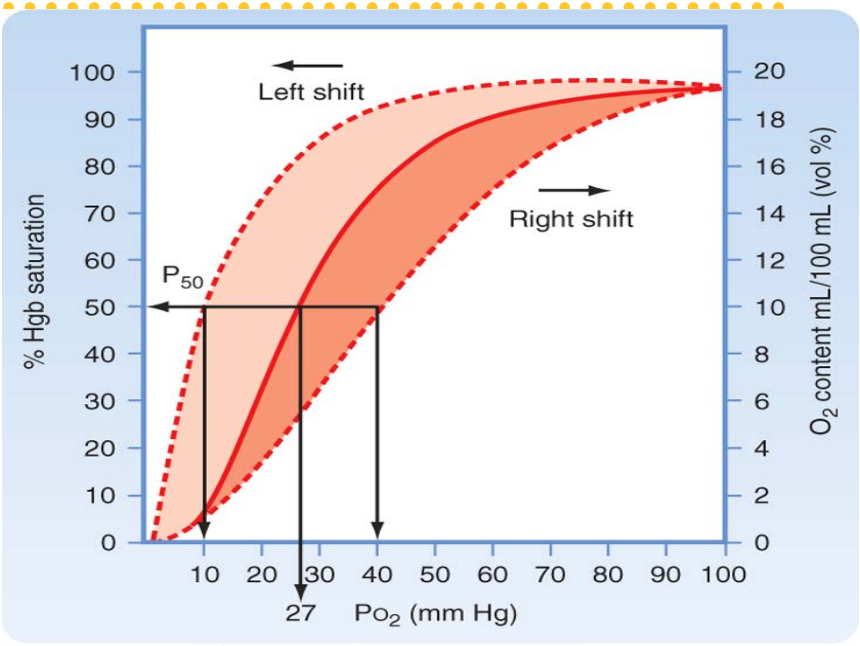
- Amino acid substitution in heme pocket: $Fe^{2+} \rightarrow Fe^{3+}$, cyanosis

- Diagnosis: abnormal SpO2, Hb electrophoresis/spectra, **metHb < 30%**
- No tx needed, cyanosis ***not*** reversible with methylene blue or vitamin C

- Distinguish from other metHbemias (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 Self-Assessment Program 6th Ed. (ASH SAP)
- ASH Pocket Guides (download from App store)
- Hematology/Oncology question bank hemeoncquestions.com/
- Hematology-Oncology board review questions www.turner-white.com/brm/bonco.htm

- Special thanks: Drs. Oyebimpe Adesina, Victor Gordeuk, Ravin Garg, and Vivien Sheehan

THANK YOU