Hemoglobin disorders

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DISCLOSURES

Agios Pharmaceuticals – Research funding, Advisory Board
<table>
<thead>
<tr>
<th>Red blood cell destruction disorders (15% of exam)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thalassemias</strong></td>
</tr>
<tr>
<td><em>Alpha thalassemia</em></td>
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<tr>
<td><em>Beta thalassemia</em></td>
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<tr>
<td><em>Hemoglobin E disorders</em></td>
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<tr>
<td><strong>Sickle cell disorders (4.5% of exam)</strong></td>
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<tr>
<td><em>Sickle cell trait</em></td>
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<tr>
<td><em>Sickle cell anemia (hemoglobin SS disease)</em></td>
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<td><img src="symbol" alt="Check symbol" /> <img src="symbol" alt="Check symbol" /> <img src="symbol" alt="Check symbol" /> <img src="symbol" alt="Check symbol" /> <img src="symbol" alt="Check symbol" /></td>
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<tr>
<td><em>Hemoglobin SC disease</em></td>
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<tr>
<td><em>Sickle cell-beta zero and sickle cell-beta plus-thalassemias</em></td>
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<tr>
<td><strong>Non-sickle hemoglobinopathies</strong></td>
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</tbody>
</table>
Globin genes and hemoglobins

Chr 11

<table>
<thead>
<tr>
<th>LCR</th>
<th>ε</th>
<th>Gγ</th>
<th>Aγ</th>
<th>δ</th>
<th>β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chr 11</td>
<td>Aα2β2 (97%)</td>
<td>Aα2δ2 (3%)</td>
<td>Fα2γ2 (&lt;1%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Chr 16

| HS40 | ζ | μ | α2 | α1 | θ |

Postembryonic hemoglobin species

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**

\( \beta^0 \) (null) = No gene product

\( \beta^+ \) = reduced production

- Excess \( \alpha \)-globin chains \( \rightarrow \) **INEFFECTIVE ERYTHROPOIESIS**
  - \( \alpha \)-globin aggregates in erythroid precursors \( \rightarrow \) intramedullary death

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

- **Membrane damage** \( \rightarrow \) **PS* exposure and hypercoagulability**
  - decreased RBC deformability
  - increased clearance from circulation

PS phosphatidylserine
Pathophysiology and complications of thalassemias

Impaired α:β globin ratio

Red cell pathology

Ineffective 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 pseudotumors

## Clinical classification of β-thalassemias

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Hb (g/dL)</th>
<th>Transf</th>
<th>Clinical features</th>
<th>Most common genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalassemia minor (trait)</td>
<td>10-12</td>
<td>No</td>
<td>No hemolysis or symptoms, RBC&gt;5million, HbA₂&gt;3.5%</td>
<td>β₀/β or β⁺/β</td>
</tr>
<tr>
<td>Thalassemia intermedia</td>
<td>7-10</td>
<td>+/-</td>
<td>high Hb F, bone disease, transfusion and/or spontaneous iron overload, splenomegaly*, pulm HTN, leg ulcers</td>
<td>β⁺/β⁺ or β⁺/β₀</td>
</tr>
<tr>
<td>Thalassemia major</td>
<td>&lt;7</td>
<td>Age&lt;2</td>
<td>&gt;95% HbF, bone disease, transfusion iron overload, splenomegaly*</td>
<td>β₀/β₀ or β₀/β⁺</td>
</tr>
</tbody>
</table>

*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 3-4 weeks
  - Goals:
    - pre-transfusion Hb: 9-10.5 g/dL
    - post-transfusion Hb: 12-15 g/dL

- **Iron chelation**
  - Initiate after 10-20 pRBCs or ferritin > 1000 ug/L
  - Single chelator or combination therapy
  - Goals:
    - liver iron concentration (LIC) < 3 mg/g
    - cardiac T2* > 20 ms
      - Cardiac iron → consider combination therapy (e.g. DFO+DFP)
# Iron chelators

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

- **Splenectomy**
  - Indications: transfusion >200-220mL/kg/year; untransfusuable 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 $\rightarrow$ 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**
### α thalassemia genetics

**Chromosome 16**

<table>
<thead>
<tr>
<th><strong>Normal</strong></th>
<th>Normal αα/αα</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Normal αα/αα" /></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Carrier: Asymptomatic</strong></th>
<th>α⁺ trait: α-/-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>WNL or isolated microcytosis</td>
<td><img src="image" alt="Carrier α⁺ trait" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>α-thal minor: Asymptomatic</strong></th>
<th>α⁰ trait --/-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild microcytic anemia</td>
<td><img src="image" alt="Carrier α⁰ trait" /> or <img src="image" alt="Carrier α⁰ trait" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Hb H Disease: Symptomatic</strong></th>
<th>Hb H disease --/-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemolytic and Microcytic anemia</td>
<td><img src="image" alt="Hb H disease" /></td>
</tr>
<tr>
<td>Splenomegaly</td>
<td><img src="image" alt="Hb H disease" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Incompatible with Life</strong></th>
<th>Hydrops fetalis --/--</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrops Fetalis</td>
<td><img src="image" alt="Hydrops fetalis" /></td>
</tr>
</tbody>
</table>
Pathophysiology of α-thalassemias

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

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:

  α thalassemia-intellectual disability 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 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 $\beta^E$-mRNA production
  ➢ precipitation of $\alpha$-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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Genotype</th>
<th>Hb EP</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb E trait</td>
<td>β^A^/β^E^</td>
<td>HbE 30%</td>
<td>Normal or low MCV</td>
</tr>
<tr>
<td>Hb E disease</td>
<td>β^E^/β^E^</td>
<td>HbE 90%</td>
<td><strong>Mild</strong> microcytic anemia</td>
</tr>
<tr>
<td>Hb E/β thal (Very common in SE Asia)</td>
<td>β^E^/β^0^ or β^E^/β^+</td>
<td>HbE 40-85%, HbF 10-60%</td>
<td><strong>Moderate to severe</strong> microcytic anemia, ineffective erythropoiesis, iron overload</td>
</tr>
<tr>
<td>Hb SE disease</td>
<td>β^S^/β^E^</td>
<td>HBE 30%, HbS 65%</td>
<td><strong>Mild sickling disorder</strong>, similar to HbS/β^+ thalassemia</td>
</tr>
</tbody>
</table>
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-β⁰ and sickle cell-β⁺ thalassemias

• Non-sickle hemoglobinopathies

• Educational resources
Pathophysiology of sickle cell disease (SCD)

- Hypoxia
- Acidosis
- Polymerization
- Sickling
- Hemolysis
- Cell adhesion
- Vaso-oclusion
- Endothelial cell
- Platelet
- Neutrophil
- HBB p.6Glu
- HBB p.6Val
- HbA
- HbS
- Nitric oxide depletion
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

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Severity</th>
<th>Characteristics</th>
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<tbody>
<tr>
<td>HbSS</td>
<td>Severe</td>
<td>Most common form</td>
</tr>
<tr>
<td>HbSβ⁰</td>
<td>Severe</td>
<td>Clinically indistinguishable from HbSS⁶</td>
</tr>
<tr>
<td>HbSO-Arab</td>
<td>Severe</td>
<td>Relatively rare⁴</td>
</tr>
<tr>
<td>HbSD-Punjab</td>
<td>Severe</td>
<td>Mostly in northern India⁶</td>
</tr>
<tr>
<td>HbSC-Harlem</td>
<td>Severe</td>
<td>Migrates like HbSC, but rare double β-globin mutation⁷</td>
</tr>
<tr>
<td>HbCS-Antilles</td>
<td>Severe</td>
<td>Rare double β-globin mutation⁸</td>
</tr>
<tr>
<td>HbSC</td>
<td>Moderate</td>
<td>25% of SCD⁹</td>
</tr>
<tr>
<td>HbSβ⁺, Mediterranean</td>
<td>Moderate</td>
<td>5%–16% HbA⁶</td>
</tr>
<tr>
<td>HbAS-Oman</td>
<td>Moderate</td>
<td>Dominant rare double β-globin mutation¹⁰</td>
</tr>
<tr>
<td>HbSβ⁺, African</td>
<td>Mild</td>
<td>16%–30% HbA⁶</td>
</tr>
<tr>
<td>HbSE</td>
<td>Mild</td>
<td>HbE found mostly in Southeast Asia¹¹</td>
</tr>
<tr>
<td>HbS-HPFH</td>
<td>Very mild</td>
<td>Large deletions in β-globin gene complex; &gt; 30% HbF⁶</td>
</tr>
</tbody>
</table>

HbA = hemoglobin A; HbE = hemoglobin E; Hbf = fetal hemoglobin; HbS-HPFH = HbS and gene deletion HPFH; HbSC = heterozygous hemoglobin SC; HbSS = homozygous hemoglobin SS; HbSβ⁰ = hemoglobin S-β thalassemia⁶; HbSβ⁺ = hemoglobin S-β thalassemia⁺; SCD = sickle cell disease.
Sickle cell trait

- HbAS $\rightarrow$ 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

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 ASFA₂ and the older SAFA₂. 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
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 2\textsuperscript{nd} 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

HCT
Gene therapy?

HbA → Transfusion
Hydroxyurea
Voxelotor

L-glutamine

Crizanlizumab
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

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**

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

ACS = acute chest syndrome; ADL = activities of daily living; QoL = quality of life; SCA = sickle cell anemia.
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%
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
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)
• Humanized monoclonal anti-P-selectin antibody that reduces cell adhesion
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
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 HbA2 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*


- Gene addition
  e.g. anti-sickling Hb (HbA$^{T87Q}$)
- Gene editing (zinc-finger nuclease, 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 \( \beta \) and \( \delta \) globin genes

- Decreased synthesis of \( \beta \)-like globins

- **Homozygote: \( \beta \)-thal major phenotype**
  - 8-30% Hb Lepore
  - 70-92% Hb F

- **Heterozygote: \( \beta \)-thal minor (trait) phenotype**
Hemoglobin Constant Spring

• Non-deletional form of α-thalassemia

• Mutation in stop codon of α₂-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: \( \text{Fe}^{2+} \rightarrow \text{Fe}^{3+} \), cyanosis

- Diagnosis: abnormal SpO2, Hb electrophoresis/spectra, \( \text{metHb} < 30\% \)
- No tx needed, cyanosis \textit{not} reversible with methylene blue or vitamin C

- Distinguish from other metHbemias (treat with \textit{methylene blue})
  - \textbf{Toxins:} nitrites, sulfanilamide, dapsone, primaquine, etc.
    - Symptomatic with metHb> 30\% (> 50\% is lethal!)
  - \textbf{Congenital deficiency in cytochrome b5 reductase:} \( \text{Fe}^{3+} \rightarrow \text{Fe}^{2+} \)
    - cyanosis improves with methylene blue or vitamin C
Other hemoglobin disorders

- **Hb with high O₂ affinity:**
  - AD, familial [erythrocytosis](#),
  - α or β-chains can be affected
  - Diagnosis: low $P_{50}$ (left shifted on O₂ dissociation curve), variant Hb in electrophoresis, DNA sequencing
  - No phlebotomy unless Ht>60%
  - Differential dx: polycythemia vera, secondary polycythemias

- **Hb with low O₂ affinity:**
  - Right shift on O₂ dissociation curve (high $P_{50} \sim 30-40$ mmHg)
  - Cyanosis, but otherwise asymptomatic (depending on degree of right shift)
  - No treatment required
Educational resources

• 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

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