Sickle Cell Disease and Other Hemoglobinopathy

**Introduction:**

1) Hemoglobinopathy is a group of diseases with abnormal structure of the hemoglobin molecule due to the genetic mutation(s) in α or β-globin chain.

2) Sickle-cell disease is the most common hemoglobinopathy due to a single point mutation in the β-globin gene, leading to the production of hemoglobin S, a less soluble protein than its normal counterpart.

**Risk Factors:**

Hereditary disease, autosomal dominant.

**Diagnosis:**

- Hb electrophoresis:
  - A, S, C, A2, F
- HbA2 measurement
- Genetic testing for mutations.

**Symptoms:**

- Hemolytic anemia
- Vaso-occlusive due to less soluble sickled hemoglobin → tissue ischemia or infarction → chronic or acute pain.
  * Sickle cell pain crisis
  * Stroke
  * Acute chest syndrome
  * Kidney infarction
  * Dactylitis or bone infarction → pain
  * Myocardial infarction
  * Priapism – (See 'Priapism' below.)
  * Venous thromboembolism
- Splenic infarction → functional hyposplenism → increased risk of infection.

**Biology:**

A. In adult, → 3 Hb forms:

- Hb A: α2 β2 (major, adult), 97%
- Hb A2: α2δ2 (minor, adult), 3%
- Hb F: α2γ2 (major, fetal), 0%
- Hb H: β4 0%

B. Human Globin Genes:

1. α-globin gene: on chromosome 16

   ------------α--α--

2. β-globin gene: on chromosome 11

   ------ Gγ--Aγ----δ----β-----

   ------------α--α--

**Pathology:**

A. Sickle cell disease (Hb SS):

- A single nucleotide mutation (A to T) of the β-globin gene results in glutamic acid (E/Glu) substituted by valine (V/Val) at position 6. Hemoglobin with this mutation is called hemoglobin S (HbS), as opposed to the normal adult HbA.
- Autosomal recessive. Homozygous is symptomatic.

**UpToDate:**

Hydroxyurea decreases sickle cell crisis, stroke and improves survival.

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B. Sickle cell trait (Hb A/S): silent carrier, asymptomatic.

C. Compound heterozygous: HbS mutation can be co-inherited with a mutation at the other β-globin alleles, resulting in sickle beta thalassemia, hemoglobin SC disease, and others.

**Prognosis:**
- Incurable, but survival improved over the years.
- Complications, especially pulmonary hypertension → decreased survival (worse prognosis).

**Clinical Pathway:**

A. Sickle Cell Disease

1) Genetics: AD. Point mutation of β-globin gene (glutamate → valine at codon 6).
   - Sickle cell trait: heterozygous (HbAS)
     * Dx: 60% HbA, 40% HbS; normal HbA2 and HbF
     * Major complications: hyposthenuria, benign hematuria (renal papillary necrosis), ↑ UTI in pregnancy, ↑ splenic infarction at high altitude.

   - Sickle cell disease: homozygous (HbSS)
     * Sx: Anemia (Hb 6-8, ↑ retic, MCV normal, + sickling cells). If low MCV, consider compound thalassemia.
     * Dx: HbS (>90%), HbF, HbA2, no HbA.
     * Major complications: pain crisis, pulmonary HTN (major cause of death).

   - Compound sickle-thalassemia diseases: → all cause sickling symptoms
     * Hb S/β(0)-thalassemia: similar to HbSS, but A2 ↑ more. No HbA
     * Hb S/β(+)-thalassemia: >60% Hb S, 10-30% Hb A (A/S ratio ≈ 15:85). → mild anemia (Hb 9-12), Sx less severe than Hb SS
     * α-thalassemia → ↓ HbS symptoms (hemolysis and cerebrovascular accident)

   - Hb SC Disease: 50% Hb S, 50% Hb C (runs as A2)
     * Sx: less anemic than HbSS, splenomegaly. Less frequent pain, but more frequent ocular and bone complications. Longer life expectancy than Hb SS

2) Major complications:
   - Infection: Parvovirus B19 (aplastic crisis); Straphy, Salmo (osteomyelitis); S. Pneumonia (meningitis); Avascular necrosis (hemoral heads, leg ulcer, etc).

   - Intravascular hemolysis: → hypercoagulable state
     * High rate hemolysis: → stroke, pulmonary HTN, priapism, leg ulcer.
     * Low rate hemolysis: → pain crisis, acute chest syndrome, osteonecrosis.


   - Acute chest syndrome: major cause of death
* Path: fat embolism (88%), in-situ thrombosis, infection. Lipid-laden macrophage on bone marrow biopsy (pathognomonic).
* Dx: new radiographic lung infiltrate (single most important criteria!), plus classic sx (chest pain, fever, hypoxia/dyspnea, acute hemolysis)
* Tx: O2; Abx; RBC transfusion (simple or exchange).
* Prevention: Hydroxyurea, Incentive spirometry.

- Pulmonary hypertension (PTH): → major cause of morbidity and mortality
  * Sx: progressive dyspnea on exertion, high-grade hemolysis (↑ LDH).
  * Dx: Echo (screening). If TRV > 3m/sec, → do right heart cath (confirmation).

- Stroke: hemorrhagic stroke and infarctive stroke.
  * Annual transcranial doppler (TCD) for screening starting at age 2-16 yrs
  * If abnormal TCD, → start chronic transfusions (monthly) → ↓ risk of stroke.
  * For acute stroke: → exchange transfusion → ↓ Hb S to <30% (RBC should be matched for ABO, C,D,E,and Kell antigens).

- Others: sickle cell nephropathy, proliferative retinopathy, splenic infarction, priapism.

3) Diff Dx of Acute Anemia:

4) Treatment: All pts need vaccination and annual eye exam.
- Hydroxyurea: → ↑ Hb F → ↓Hb S sickling, ↓ stroke, ↓ pain crisis, → ↑OS
  * Indicated for > 3 painful episodes/year; history of ACS, severe anemia, or stroke prevention if chronic transfusion is NOT possible.
- Treat iron overload.
- Blood transfusion:
  * SIMPLE transfusion: → acute need to ↑ O2
  * HYPER (chronic): → stroke prevention
  * EXCHANGE: → Acute stroke, acute retinal artery occlusion, priapism → ↓ HbS to <30% and ↑ Hb to 9-10.
  * SIMPLE or EXCHANGE: → Acute chest syndrom (ACS)
- Inappropriate indication for blood transfusion:
  * Chronic anemia, uncomplicated pain episodes, infections, minor surgery not needing general anethesia, aseptic necrosis, uncomplicated pregnancy

5) Peri-op management:
- Keep Hb >10g/dl with SIMPLE transfusion for surgeries requiring general anesthesia
  - For SC disease, → exchange transfusion
  - Hydration, and incentive spirometry
  - Preventative measures for surgery:
* Minor surgery: → Simple RBC transfusion.
* Major surgery: → Exchange transfusion
* Pregnancy: No data to support prophylactic transfusion.

C. Compound Thalassemia-Hemoglobinopathy:
- HbS-β-thalassemia; HbS-α-thalassemia
- Hemoglobin E/β-Thalassemia: SE Asia. Hb E 60-85%, Hb F 15-40%
  * Mild to moderate microcytic hemolytic anemia; Ineffective erythropoiesis; iron overload.

D. Hemoglobin E (β26 glu → lys): this mutation → ↓ β chain production (thalassemic effect)
  - Sx: Hb Trait (A/E): 30% HbE, no anemia, microcytic, target cells
  * Hb E Disease (E/E): 90% HbE, mild anemia, microcytic, target cells (many)
  * Hb E-β-thal (E/β(0)): → significant thalassemia (HbE 40-85%, HbF 10-60%), ↓↓ MCV.
  * Hb SE (S/E) ≈ Hb S-β-thal

E. Hemoglobin C (β6glu → lys): crystal aggregate in RBC → ↓ RBC survival.
  - Sx: Hb C, co-migrates with Hb A2 and Hb F in Hb electrophoresis.
  * Heterozygous (trait): clinic normal, no anemia, some target cells
  * Hb CC (homozygous) , Hb C/β-thal: mild hemolytic anemia, splenomegaly
  * Hb SC: Hb C crystal does not involve in HbS polymerization, → HbSC less severe than Hb SS, but has higher incidence of peripheral retinopathy.

F. Hb D: codon 121 of β globin gene. Major clinical relevance is that compound heterozygote with HbS can cause sickle cell disease.

G. Congenital Heinz body Anemia: AD (rare)
  - Defective heme binding to globin → form unstable Heinz body → early RBC destruction
  - Dx: Hb electrophoresis (normal); Heinz body (crystal violet, isopropanol test).
  - Tx: avoid oxidant agents, folic acid, blood Tx, splenectomy for severe hemolysis.

H. O2 Affinity Variants:
1) High O2 affinity Hb mutant: → erythrocytosis
   - Low P50 (relative tissue hypoxia) → High affinity, left shift O2 dissociation curve (nl 2,3-DPG)
   - Familial erythrocytosis: high affinity genetic mutant, autosomal dominant
     * Dx: ↓ P50 (low) → identify globin gene mutation
     * Tx: erythrocytosis usually mild, phlebotomy NOT necessary
   - Carboxyhemoglobinemia: CO poisoning → O2 bind tightly and do not release (acquired high affinity) → functional hypoxia
     * Sx: rapid progression → loss of consciousness, coma, seizure and death
     * Tx: 100% O2 or hyperbaric oxygen
2) Low O2 affinity Hb mutant: → asymptomatic cyanosis, anemia
   - High P50 → Low affinity, right shift O2 dissociation curve
   - Hemoglobin M (Methemoglobinemia): Low affinity mutants
     * Structural mutation (AD) → "ferrous heme → ferric heme" → unable to bind and transport O2 → cyanosis (NO desaturation). Asymptomatic. Cyanosis NOT improved with Meth Blue, VitC because of structural change.
     * NADH diaphorase deficiency (cytochrome b5 reductase) (AR) → defective enzymatic reduction from Fe(3+) to Fe (2+) → cyanosis, "chocolate brown blood", a/w neurological abnormalities. Cyanosis IMPROVED with Meth Blue, VitC.
       - Clinical: 10-20% (visible cyanosis); >30% (headache, dizziness, dyspnea, tachypnea, tachy); >50% (stupor and obtundation), >70% (lethal)
       - Tx: Mild case → Ascorbic Acid;
         * Severe case (>40%): Methylene Blue, 1mg/kg IV over 5min, q 4-6 hrs. Methylene Blue should be avoided in G6PD deficiency. In that case or in case of nitrate exposure, can use high-flow oxygen or hyperbaric oxygen.

Follow-Up:

1) Sickle Cell Disease:
   - UA, Pulse Ox,
   - Rinal exam by ophthalmologist (annual screening),
   - Ferritin for iron overload,
   - Echo for pulmonary hypertension.

Pharmacology:

A. Deferasirox (Exjade): PO. 20mg/kg, daily. FDA approved for iron overload from transfusion.
   - SE: kidney failure, cytopenia, hepatic abnormality, ocular and auditory disturbance, Yersinia infection (board q), growth delay.

B. Deferoximine (Desferal): IV (prolonged infusion)

C. Hydroxyurea