Objectives

- Physiology
- Manifestations and treatment
- Why?
Pathophysiology:

- Vaso-occlusive disorder
- Hemolytic disorder
- Severity of disorder dependant on inheritance pattern:
  - Autosomal recessive
  - HbSS most severe
  - Hb AS- intermediate
  - coexisting alpha/beta thalassemia
  - Carriers tend to be benign

Normal HbA, HbAS/SC (~50% sickled) spontaneous bleed (nose), impaired ability concentrate urine, rarely, crises but higher case of retinopathy; those with certain thalassemia have more HBA and less disease; Carriers less susceptible to malarial infection due to balanced polymorphism;
The Sickle Cell

- Hemoglobin S
  - Valine for glutamic acid in 6th A.A. Beta globin gene
  - De-oxygenation
  - Distortion of erythrocytes into crescent (sickle) shape
  - Mean life span = 17 days
  - Adherence to endothelium

A23b2 tetramer: Polymerization leads to elongated rope-like fibers on cell surface which align. Crescent shape causes deformability, decreased solubility, hemolysis, and inability to pass through microvascular circulation. Immunoglobulin coat the rbc causing phagocytosis; normal 100 days.
Epidemiology

- High risk population: African, Mediterranean, Middle Eastern, Indian, Caribbean, Central American
- 8% of African Americans carry gene; 0.17% of whites
- SCD accounts for 75,000 hospitalizations per year
- Mean age of death:
  - 42yrs for Males and 48 for females with SS disease
  - 60yrs and 68yrs for all SCD
- 4000-5000 pregnancies a year with SS disease
- 30% of all mortality associated due to acute events
Labs:

- Mild / moderate normochromic anemia - Mean value of Hb 7.9 g/dl
- Abnormal LFTs
- Elevated LDH
- Normal to high MVC
- Low serum haptoglobin
- High WBC (pt. < 10yrs)
- High platelet count (pt. < 18yrs)

; platelet, bilirubin, wbc not elevated in HbAS & Sickle cell-beta thalassemia. Hyposplenia due to repeated infarction
Smear:
- sickled red cells
- Polychromasia- 3 to 15%
- Howell-Jolly bodies

(reflects hyposplenia)
round, purple staining nuclear fragments of DNA in the red blood cell
Diagnosis

- Prenatal testing: chronic villus sampling at 8-10 weeks gestation
- Universal screening
  - targeted screening
  - Heel stick filter paper screen within 72 hours of births
  - 29.91/10,000 African American; 0.11 white; 0.29 Hispanic

Early recognition decrease mortality 25% to 3% 1-5 yrs, specifically bacterial infections; second one at 1-2
Pregnancy and Fetal Complications

- Increased risk for
  - Spontaneous abortion
  - Pre-eclampsia
  - Fetal death
  - Preterm deliveries
  - And low birth weight

- Maternal complications: pyleonephritis, endometritis, thrombus, C-section

- Base iron replacement on basis of iron studies

During pregnancy, higher metabolic demands, hypercoag state, vascular stasis, transfusions and hemolysis increases iron stores; controversial: use of transfusions in pregnancy prophylactically.
- Honeymoon period in first few months
- Homozygous disease symptoms are present in:
  - 96% of children by age 8
  - 61% by age 2
  - 32% by age 1
- Most common ages of death in children is 4-6 yrs
- Associated with growth failure and delayed puberty
- Hypopituitarism, hypogonadism
Dactyliitis

- Most common initial symptom
- acute pain in hands and/or feet
- warmth/redness
- raised ESR
- resembling osteomyelitis
- Tx: hydration, analgesia, warm compresses, SQ tebutaline 0.25-0.5mg

The first symptom in long list of “clotting” or vasoocclusive phenomenon. Symptom for 50% of kids by age 3; other tx options- hyperbaric o2 and transfusion; kids can develop avascular necrosis of the digits
Priapism

- Occurs in 6-42% of males
- Peaks 5-13yrs and 21-29yrs
- Due to increased hemolysis and decreasing availability of nitric oxide
- Scarring may result in impotency
Acute Anemic Crisis

- Hyperhemolytic crisis
  - Sudden exacerbation of anemia with reticulocytosis
  - Rare with unknown cause - precipitants include infection and Drugs
  - High platelet count, reticulocyte count, indirect bilirubinemia, elevated LDH
  - TX: transfusion, fluids, analgesics, folic acid, Abx

Infections and drugs/substances cause early destruction of RBC (moth balls, fava beans, aspirin, phenacetin, sulfonamides, chloroquine, methyl blue).
Aplastic Crisis

- arrest of erythropoiesis lasting 5-10 days
- Infection with human parvovirus B19
- Others: Strep Pneumonia, Salmonella, Epstein Barr
- More common in children
- Tx: Acute transfusion therapy
  - Respiratory isolation
  - O2
  - ABX

Leads to decrease in Hb, red cell precursors and reticulocytes(<10,000/mcl) in peripheral blood; over 60% of SCD children show evidence of B19 infection by age 15 (invades proliferating erythroid progenitors); reticulocytes reappear within 12-14 days;
Splenic sequestration

- vaso-occlusion leads to splenic pooling of RBC
- Sudden weakness, pallor, tachycardia, tachypnea, abdominal fullness
- Splenomegally
- Hb drops at least 2g/dl
- Risk of hypovolemic shock, especially in children
- Risk of Parvovirus B19 infection
- 30% incidence and 20% have as initial symptom
- 10-15% mortality rate and recurs in 50% of survivors
- **Tx:** high flow O2, Fluids, transfusion, abx, splenectomy

occurs most commonly in child <2yrs; occurs in non-fibrotic spleen; persistent reticulocytosis and thrombocytopenia
Acute Painful Episodes (ACP)

- Formerly Sickle Cell Crises
- 1st symptom in 25% of pt after 2 yrs of age
- Episodes last 2-7 days
- Frequency peaks at 19-39 yrs
- Most have no cause
- Precipitated by Hb > 8.5 g/dl, cold, dehydration, infection, stress, menses, alcohol, sleep apnea
- Any area of the body may be affected
- 50% of episodes accompanied by fever, swelling, tenderness, hypertension, nausea, tachypnea
- Recurrence leads to depression, apathy and despair
APC continued…. 

- Labs are unhelpful 
- Acute multi-organ failure syndrome 
- 3 or more episodes correlates to higher mortality 

**Management:**
- Hydroxyurea 
- 02 for documented Hypoxia 
- Hydration: IV in severe cases 
- Analgesia- morphine 0.1-0.15mg/kg q3-4hrs

Some new indicators of the density distribution of the SC in predicting episodes; acute phase reactants( esp, fibrinogen, LDH) are raised during the evolution of the crisis; ( can cause erythroid hypoplasia).Hydroxy urea reduces sickle HB and promotes fetal HB; Avoid meperidine and ketorolac. normalize electrolytes – use D5- NS
Infections

- Major cause of morbidity and mortality
- Absence of normal splenic function leads to susceptibility to encapsulated organism

- Bacteremia
  - Most common Strep Pneumoniae followed by H. Flu
  - Leukocytosis with left shift
  - Aplastic crisis +/- DIC
  - 20-50% mortality- decreased since the pneumococcal vaccine

dysfunctional antibodies and complement, less common in HBAS as still tend to have functioning spleens in childhood,
- **Meningitis**
  - Primarily a problem in infants and young children
  - S. Pneumoniae most common cause
  - Frequently in bacteremia (50%)

- **Bacterial pneumonia**
  - Mycoplasma, chlamydia pneumonia- 20%
  - Legionella, Strep. Pneumonia and H. Flu uncommon
  - Present with typical symptoms

- **Osteomyelitis**
  - Common in infarcted bone and long bones
  - Salmonella most common cause

Often newborns on prophylaxis; Infection in multiple sites of the bone; Aureus <25% of osteomyelitis; leg ulcers are common and often very painful and infected (associated with DVT)
Bone Complications

- Involved due to accelerated hematopoiesis and bone infarction
- **Osteonecrosis** (aseptic necrosis) - infarction of bone trabeculae and marrow cells
  - femoral and humeral heads
  - Worsening pain on motion, limitation in motion
  - Early films are negative, later, joint space narrowing, segmental collapse
  - **TX**: avoid weight bearing, analgesia for 6 months

Accelerated hematopoiesis leads to bossing of forehead, fish mouth deformity of vertebrae and chronic tower skull
- **Marrow infarction**
  - pain, tenderness, swelling
  - Resolves in 1-2 weeks
  - Reticulocytopenia, exacerbation of anemia, pancytopenia
  - Films: mottled, strand like increases in density distributed randomly in medulla
  - **Tx:** narcotics, hydration, NSAIDS

Might have to do bone scans to distinguish from osteomyelitis; Can lead to fat embolism
Acute Chest Syndrome

- pneumonia, infarction, fat embolism
  - Occurs in 30-50% of pt.
  - **Tx**: antibiotic (for atypicals and community acquired)
    - O2 (keep sat >92%),
    - analgesia
    - volume repletion/exchange transfusion

- Chronic: restrictive/obstructive lung disease, hypoxemia, pulmonary hypertension

Presents as CP, new infiltrate (UPPER/MIDDLE), fever; infection more common in children; transfusion to lower HBs <30% CHILD, <50% ADULT; may use anticoagulation with heparin if PE; Heme consult; Asthma more common in SCD
Cardiac Complications

- Increased cardiac output secondary to chronic anemia leading to LVH and cardiomegaly
- High output cardiac failure
- Acute myocardial infarction

In absence of CAD at about 10% rate on autopsy; due to exceeding limited oxygen carrying capacity;
Cerebrovascular Events

- 25% of pt develop
- TIA, stroke, intracerebral hemorrhage, spinal cord infarction/compression
- Risk of stroke is 15% by age 20, 24% by age 30
- Silent strokes in 10-20%
- related to low Hb & increased BP
- Recurrence is common secondary to fragile dilated vessels

Vestibular dysfunction and sensory hearing loss uncommon; Ts includes immediate exchange transfusion HbS to<30%
Hepatobiliary Complications

- Cholelithiasis
  - Pigmented gallstones
  - Occurs as young as 3yrs
  - Found in 70% of patient
  - Cholecystectomy is performed with high morbidity (with complication rate of 39%)

Chronic liver disease (hepatomegaly secondary intrahepatic trapping), Hep C infection, autoimmune liver disease and transfusion associated liver disease
Renal Complications

- vasa recta capillaries of medulla
- Painless hematuria (papillary infarcts/necrosis)
- Renal colic
- Nephrogenic diabetes insipidus
- Focal glomerulosclerosis and ESRD (5-18% of SCD pt)
- Renal medullary carcinoma
- Iron renal loss can lead to Iron deficiency anemia (20% SCD)

Low O2 tension/high osmolality dehydrates RBC; Increasing HbS; Anemia worsened by lack of EPO when renal disease develops; Present with decreased urine; treat hypertension with ace inhibitors
Ophthalmic Complications

- proliferative retinopathy
- retinal artery occlusion
- retinal detachment
- proliferative sickle retinopathy

Comma-shaped vessels in conjunctiva, iris atrophy/neovascularization, dull-gray fundus, retinal venous tortuosity, nonproliferative retinal hemorrhage.; Black sunburst retinal pigment hyperplasia 2 to vasoocclusion, hemosiderin-laden macrophages
Additional Measures

- Regular physician appointments for baseline labs
- Palpation to avoid fatal splenic sequestration
- S. Pneumoniae, H. Flu, Hep B., influenza Immunization
- Prophylactic Penicillin
  - 125mg BID until 2-3 years
  - 250mg BID from 3 to 5 years
- Folic acid 1mg/day to avoid megaloblastic anemia
- Retinal evaluation beginning at childhood
- Pelvic examinations/birth control
- Hematopoietic cell transplantation

Routine HTNABX prophylaxis stopped after 5 yrs unless serious pneumococcal infection or splenectomy. Multi Vitamin deficiencies in SCTX vit d, iron); studies suggest inhaled NO will increase O2 affinity of SC; transplant only for those <16yrs and HLA matched.