Sickle Cell Disease

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Disclaimer

- Member of DSMB for MAST
Objectives

- To become acquainted with sickle cell center expertise in caring for patients with sickle cell disease
- To become familiar with the Newborn screening results
- To understand the role of the primary care provider in the care of patients with Sickle Cell Disease
- To become familiar with clinical complications in sickle cell children and adolescents

Sickle Cell Disease

- How Common is it?
  - In the US Pediatric population the prevalence of
    - Diabetes Mellitus 1:2,500
    - Acute Leukemia 1:2,880
    - Cystic Fibrosis 1:2,940
    - Muscular Dystrophy 1:5,000
    - Phenylketonuria (PKU) 1:10,000
    - Galactosemia 1:17,000
SCD Incidence

- In the US, Sickle Cell Disease affects
  - 1 in every 400 African Americans
  - 1 in 1,000-1,400 Hispanics
  - 1 in 3,000 Native Americans
  - 1 in 60,000 Whites

  (1993, AFHCPR data)

SCD Incidence

- Disease Impact in our Country
  - Most common genetic defect in the US (autosomal recessive)
  - 100,000 people with SCD in the US
  - 5,000 affected infants born in US each year
    - Hb SS 65%
    - Hb SC 25%
    - Hb Sβ+ Thalassemia 8%
    - Hb Sβ0 Thalassemia 2%
World-Wide Distribution of Hemoglobin S

Geographic distribution of hemoglobin S in the world

What Is Sickle Cell Disease?

- An inherited disease of red blood cells
- Affects hemoglobin
- Polymerization of hemoglobin leads to a cascade of effects decreasing blood flow
- Tissue hypoxia causes acute and chronic damage
Why Do Cells Sickle?

- Point of mutation on β-globin chain of hemoglobin: Glutamic acid is substituted for valine
- Allowing the polymerization of sickle hemoglobin when deoxygenated

Normal vs. Sickle Red Cells

**Normal**
- Disc-shaped
- Deformable
- Life span of 120 days

**Sickle**
- Sickle-shaped
- Rigid
- Life span of 20 days or less
Hemolysis and Vaso-occlusion

**Hemolysis:**
The anemia in SCD is caused by hemolysis, and the degree of anemia varies widely between patients.

The production of red cells by the bone marrow increases dramatically, but is unable to keep pace with the destruction.

**Vaso-occlusion:**
Occurs when the rigid sickle shaped cells fail to move through the small blood vessels, blocking local blood flow to a microscopic region of tissue.

Amplified many times, these episodes produce tissue hypoxia. The result is pain, and often damage to organs.

**Sickle Cell Manifestations**

**Acute Manifestations**
- Bacterial sepsis or meningitis*
- Recurrent vaso-occlusive pain (dactylitis, musculoskeletal or abdominal pain)
- Splenic sequestration*
- Aplastic crisis*
- Acute chest syndrome*
- Stroke*
- Priapism
- Hematuria, including papillary necrosis

**Potential cause of mortality**

**Chronic Manifestations**
- Anemia
- Jaundice
- Splenomegaly
- Functional asplenia
- Cardiomegaly and functional murmurs
- Hyposthenuria and enuresis
- Proteinemia
- Cholelithiasis
- Delayed growth and sexual maturation
- Restrictive lung disease*
- Pulmonary hypertension*
- Avascular necrosis
- Proliferative retinopathy
- Leg ulcers
- Transfusional hemosiderosis*
**SCD Incidence**

- **Is Newborn Screening Necessary?**
  - All 50 states have a newborn screening program to detect sickle cell disease!
  - 1 in 10 African Americans carry one gene (sickle trait)

**Newborn Screening for Sickle Cell Disease**

- Currently 47 states, Washington DC, Puerto Rico, and the Virgin Islands provide mandatory universal newborn screening
- Specimen must be drawn prior to transfusion
- Prevention of pneumococcal septicemia
- Early Detection and treatment of splenic sequestration

Linkage to timely diagnostic, parental education, and comprehensive care markedly reduces morbidity and mortality in infancy and childhood.
**Constituents of Hemoglobin**

- Hemoglobin has 2 Alpha and 2 Beta chains
- Normal hemoglobin in the red cell consists of Hb A, Hb F, and Hb A2
- Chromosome 11 encodes DNA sequences for beta (β), delta (δ) and gamma (γ) chains
- Chromosome 16 encodes DNA sequences of alpha (α) chains
- The beta variants such as Hb S, Hb C, and Hb D all occur from a mutation on Chromosome 11 causing a defective beta globin gene

**Normal Newborn Screening**

FA
F = Fetal hemoglobin 80-90%
A = Normal A hemoglobin 10-20%
**Hemoglobin S**

- Valine substitutes for glutamic acid on position 6 of Beta globin chain
- Sickle Hb polymerizes with deoxygenation causing distortion of RBC, leading to vasoocclusion and eventual hemolysis

**Newborn (NBS) Screening Results**

- Hemoglobins are listed in order of percentage
- Sickle Cell Trait
  - FAS
- Sickle Cell Disease
  - FS
  - Electrophoresis shows absence of α1, normal α2 and F; and presence of Hb S
Newborn Screening in Missouri

- All significant hemoglobinopathies are screened in Missouri.
- Greater responsibility is placed on the physician of record.
  - Inform and educate parents.
  - Recommend additional appointments to a sickle cell expert.
- All SCA infants should be started on prophylactic penicillin by the age of 2 months.
- All parents are instructed to seek medical attention when there is a fever of ≥ 101.5°F.

Hemoglobin C

- Lysine substitutes for glutamic acid in position 6 of Beta globin chain (Chromosome 11).
- Higher frequency among Western Africa, Italy, Greece, Turkey, and the Middle East.
- Hb C crystalizes within the red cell.
- The presence of Hb C results in increase viscosity of the blood.
NBS Results

- C trait
  - FAC
- CC hemoglobin
  - FC
    - Shortened red cell survival (hemolysis) in HbCC
- SC disease
  - FSC
    - Sickling complications

Beta Thalassemia

- Absence or decrease of one or more beta globin genes
  - Decreased production of normal Hemoglobin A (Chromosome 11)
  - Microcytosis
  - Unbalance synthesis of alpha and beta globin chains
  - Ineffective erythropoiesis and a hemolytic anemia
NBS Results

- Beta thal major: fatal in early childhood w/o PRBC transfusions
  - Splenomegaly
  - Significant red cell dyscrasia
- Beta thal intermedia: severe microcytosis; +/- PRBC
  - HEP: Hb F, Hb A₂, ↑ Hb A is absent (Beta₀) or markedly ↓ (Beta⁺)
- Beta Thalassemia Minor/Trait: heterozygotes for one abnormal beta globin gene
  - Mild microcytic anemia
  - HEP: + Hb A, slight ↑ Hb A₂, normal or slightly ↑ Hb F and ↑ RBC count

Alpha Thalassemia

- Loss of > one alpha globin genes (Chromosome 16)
- A normal person has four alpha genes (αα/αα)
- Alpha thal major: lack of all four alpha genes
  - Hydrops fetalis; usually fatal in utero (---/---)
- Hemoglobin H disease: loss of three alpha genes
  - Moderately severe hemolytic anemia (-α/---)
- Alpha thal trait: two alpha genes lost
  - Mild anemia with microcytosis; resembles Fe deficiency; normal A2 (α-/α-) or (---/αα)
Hemoglobin Bart’s

- Silent carrier alpha thal: one alpha gene lost
  - Not clinically significant
  - Hb Bart’s on newborn screen (α-/αα)
- Hb Bart’s in cord blood sample may indicate the number of alpha genes lost
  - <5% = most likely one gene deletion; silent carrier alpha thal, (-α/αα)
  - 5-10% = alpha thal minor, loss of two alpha genes (-α/-α) or (-/-αα)
  - >10% (usually 15-20%) = more severe form of alpha thal; further testing is indicated (-/-α)

Newborn Screening Results

- Confirmation of NBS by HEP must be done
- Genetic counseling for “traits” by PCP, Sickle Cell Foundation or hematologist
- Absence of Hemoglobin A1 confirms it is NOT sickle cell trait
- [www.SCInfo.org](http://www.SCInfo.org): info on NBS results
- Hb F modifies severity of SCD
- Alpha thalassemia trait modifies SCA severity
Newborn Screening Results

- FS (Sickle Cell Anemia Hb SS)
- FS (Sickle beta-0 Thalassemia, no beta globin)
- FS (Sickle Hereditary Persistence of Fetal Hemoglobin HbHb)
- FSC (Hemoglobin SC Disease, Hb SC)
- FSA or FS (Sickle beta -+ Thalassemia, reduced beta-globin)
- FC (Hemoglobin C Disease, may have hemolysis)
- FAS (Sickle Cell Trait, must do genetic counseling)
- FA (Normal newborn screen)
- FAX or FX (Abnormal hemoglobin present, MUST have confirmatory testing done)
- F (Homozygous beta Thalassemia)

Significant Causes of Morbidity/Mortality in Children with Sickle Cell Disease

- Aplastic Crisis
- Splenic Sequestration
- Stroke
- Acute Chest Syndrome
- Painful Episodes
- Serious Infection
Role of the Primary Care Physician

- ENCOURAGE COMPREHENSIVE CARE AND MEDICAL HOME
- Check the Newborn Screen Results!!
  - Start PCN 125mg BID if suspect SCA
  - Refer to hematology
- Offer genetic counseling for AS, AC, AD
  - Impaired urine concentration – AS
  - Gross Hematuria – AS
  - Splenic infarct at high altitudes – AS
  - Rhabdomyolysis during prolonged strenuous exercise - AS

Fever and Infection

- Fever > 38.5° C (101.5° F) is an EMERGENCY
- 33% <5y Hb SS will become septic without PCN prophylaxis
- Basic laboratory evaluation (consider):
  - CBC with differential and reticulocyte count, blood, urine, and throat cultures, urinalysis, chest x-ray
- Indications for hospitalization & IV antibiotics
  - Child appears ill
  - Any temperature > 40° C
  - Abnormal laboratory values
- Start IV antibiotics IMMEDIATELY if child appears ill or temperature > 40° C
  (DO NOT WAIT FOR LABS)
Hyposplenism

- Functional reduction of splenic activity
  - Intrasplicenic sickling \(\rightarrow\) altered circulation \(\rightarrow\) splenomegaly \(\rightarrow\) progressive fibrosis \(\rightarrow\) autosplenectomy
    - May see Howell-Jolly bodies on smear
- Infection risk
  - 300-600x more likely to develop overwhelming pneumococcal and H. influenzae sepsis/meningitis
  - Also linked to increased risk of gram-negative enteric organisms and Salmonella
  - Greatest risk is during the first 5 years of life!!

Current Recommendations

- Antibiotic prophylaxis
  - Hgb SS and Hgb Sβ° thalassemia patients
    - Pen VK
      - 0-3 yo: 125mg PO BID
      - 3-11 yo: 250mg PO BID
      - ≥ 12 yo: 500mg PO BID
    - Alternative = Erythromycin
  - Typically stop at 5 yo @ CMH (other centers may vary)
    - Longer if surgical splenectomy or pneumococcal sepsis
Splenic Sequestration

- Sudden trapping of blood within the spleen
- Usually occurs in infants under 2 years of age with SS
- Spleen enlarged on physical exam, may not be associated with fever, pain, respiratory, or other symptoms
- Circulatory collapse and death can occur in less than thirty minutes

- Recurrence very common (50%)
- Associated with high mortality (20%)

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**Splenic Sequestration**

- **Hemoglobin SS**
  - Incidence increased: 6 and 36 months
    - Overall incidence about 16%
  
  
- **Hemoglobin SC**
  - Incidence increased: 2 and 17 years
    - Mean age 8.9 years
    - Can occur in adolescence and adulthood
    - Incidence about 5%
Treatment For Splenic Sequestration

- Intravenous fluids
  - Maintain vascular volume
- Cautious blood transfusion
  - Treat anemia, sequestered blood can be released from spleen
- Spleen removal or splenectomy
  - If indicated

**Splenic Sequestration**

- Splenic Sequestration Crisis
  - Rapid splenic enlargement
  - Rapid fall in hemoglobin level
  - Fall in Platelet counts
  - Presence of Nucleated Red Blood Cells
  - Usually febrile and sometimes listless
- Treatment
  - Close monitor VS, Hb
  - Hydration and transfusion acute and chronic
  - Teach spleen palpation
Pneumonias and Acute Chest Syndrome

- Acute Chest Syndrome
  - New pulmonary infiltrate on chest radiograph
  - +/- chest pain
  - +/- low oxygen level
  - 2nd cause for hospitalization
  - 25% of all deaths in SCD
  - Increased association with asthma/atopy
  - Occurs frequently during or after painful episode

- May be associated with emerging pulmonary hypertension

Treatment
- Antibiotics
- Bronchodilator/bedside incentive spirometry
- Respiratory toilet
- Careful pain control
- Transfusions

Acute Chest Syndrome
A leading cause of death in sickle cell disease

- Clinically:
  - Acute onset of fever, respiratory symptoms, new infiltrate on chest x-ray

- Definition:
  - Acute onset chest symptoms AND new infiltrate on CXR, fever, tachypnea, cough, new onset hypoxia, increased WOB, chest pain

Since you cannot distinguish between acute chest syndrome and pneumonia clinically there is no change in treatment.
Strokes

- 10% of children with Hb SS
- 300 x risk of normal children
- Mostly between ages 3-12 years
- 70% risk of reoccurrence without chronic transfusion therapy
- Treatment is chronic transfusions
- May be “silent” manifesting only as learning difficulties or headaches (22%)

Stroke

- Peak incidence b/w 5-10 yo
- Underlying arterial stenosis or obstruction
  - Internal carotid, MCA or ACA
- Diagnosis: diffusion-weighted MRI, FLAIR, MRA
- Treatment: exchange transfusion therapy to maintain sickle hemoglobin at or below 30%
Stroke

- Intracranial hemorrhage
  - More common in adults
- Sequela overt and “silent strokes”
  - Paralysis: overt stroke
  - Neuropsychologic changes: both overt and silent strokes
    - Visual-spatial impairment
    - Impaired memory
    - Poor impulse control

Stroke

Any acute neurologic symptom other than mild headache, even if transient, requires urgent evaluation.

- Surveillance/prevention
  - TCD monitoring annually
    - Start at 2 years-old
    - Initiate treatment for persistently $>200$ cm/sec
  - Chronic transfusion therapy
Transcranial Doppler (TCD) uses ultrasound to examine the arteries, measure blood flow, and look for signs of vasospasm.

Courtesy of Mayfield Clinic / University of Cincinnati Department of Neurosurgery, Ohio
Indications for Simple/Acute Transfusion

- Pre-operatively (Goal to ↑ hemoglobin ≥ 10gm/dL)
- Stroke (initial presentation)
- Acute Chest Syndrome (initial presentation)
- Aplastic Anemia
- Splenic sequestration
- Symptomatic anemia
- Priapism

Indications for Chronic Transfusions

- Cerebral Vascular Events (stroke) → Secondary Stroke Prevention
- Abnormal Transcranial Doppler (TCD) → Primary Stroke Prevention
- ?? Silent Infarct
- Recurrent Splenic Sequestration
- Recurrent Acute Chest Syndrome
- Recurrent Intractable Pain
Pain Guidelines

- Still the hallmark of sickle cell disease
- All pain is not sickle cell pain episode
- 20% - frequent pain
- 30% - rarely have pain
- 50% - one pain episode per year

- Painful episode (vasoocclusion episode)
  - Hydration and
  - Anti-inflammatory
    - NSAID
  - Narcotics
    - Oral or parenteral

- Observe for respiratory compromise

Pain Management

- Pain is an emergency

- Hospital evaluation:
  - Hydration: 1.5 times maintenance unless acute chest syndrome suspected
  - Assess pain level and treat
    - Do not withhold opioids
    - Frequently reassess pain control
  - Assess for cause of pain/complications
Pain Management

Mild – moderate pain
- Acetaminophen
  - Hepatotoxic
- Non-steroidal anti-inflammatory agents (NSAIDs)
  - Contraindicated in patients with gastritis/ulcers and renal failure
  - Monitor renal function if used chronically

Pain Management

Moderate or less severe pain
- Opioids are first-line treatment
- Morphine sulfate or hydromorphone
- Meperidine NOT recommended
  - (Metabolite causes seizures & renal toxicity)

Moderate – severe pain
- Acetaminophen or NSAIDs in combination with opioids
- Other adjuvant medications (sedatives, anxiolytics)
  - May increase efficacy of analgesics
Other Complications of Sickle Cell Disease

- Aplastic crisis
- Priapism
- Retinopathy
- Pulmonary hypertension
- Sleep apnea
- Cardiomyopathy, heart failure
- Gall stones, Cholecystitis
- Enuresis
- Avascular necrosis, early osteoarthritis
- Infarcts – bone, organs
- Skin ulcers
- Increased fetal loss
Hydroxyurea

- Promotes production of Hb F
- Even a small increase in Hb F can retard sickling
- ↓ inflammation, ↓ hemolysis
- ↓ metabolic rate
- Few side effects (mild neutropenia, thrombocytopenia, hair loss)
- Treatment with Hydroxyurea has been shown to reduce pain events, hospital admissions and the need for blood transfusions by 50%
- 15 years experience in adults, not experimental

Multicenter Study of Hydroxyurea in Sickle Cell Disease

<table>
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<th>Event</th>
<th>Hydroxyurea (n = 152)</th>
<th>Placebo (n=147)</th>
<th>P value</th>
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<td>Pain events/year</td>
<td>2.5</td>
<td>4.6</td>
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<td>Hospitalizations/year for pain</td>
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<td>2.5</td>
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<td>Episodes of ACS</td>
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<td>.003</td>
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<td>Patients transfused</td>
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<td>79</td>
<td>.002</td>
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<tr>
<td>Transfusion units</td>
<td>423</td>
<td>670</td>
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Hydroxyurea Effect
Peripheral Smear

Pictures courtesy of Dr. Russell Ware, St. Jude Children’s Research Hospital. How I use hydroxyurea to treat young patients with sickle cell anemia. Blood. 2010; 115(26):5306.

Sickle Cell Disease and BMT

- Bone Marrow Transplant
  - Substitutes normal red blood cell progenitors from ‘donor’
  - Requires high dose chemotherapy to prevent rejection
  - Donor source either BM or CB
  - Mixed chimera enough to modify course of disease, full ablation may not be needed
  - Success 90% cure, 5% relapse and 5% risk of death
### Myeloablative Matched Sibling BMT for Sickle Cell Disease

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<th>Worldwide</th>
<th>Walters</th>
<th>Atlanta</th>
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<td>175</td>
<td>55</td>
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<tr>
<td>Survival</td>
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<td>95%</td>
<td>96%</td>
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<td>DFS</td>
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<td>Rejection</td>
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<td>9%</td>
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<td>10%</td>
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<td>cGVHD</td>
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<td>11%</td>
<td>8%</td>
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### Recent and Current Studies

- BABY HUG (Prospective HU in <18mo)
- SWITCH (Transfusion to HU for CVA)
- SITT
- TWITCH
- Glutamine
- Anti-Platelet Drugs
- Neuroprotective Study
- Vasodilators for Pulmonary Hypertension