Adult SCD Complications and Treatments
Shift and Paradigm

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Case presentation 1

32 yo AA F;  Hgb SS

Hx:
- CVA w transient hemiparesis -16 yo
- Recurrent ACS/Pneumonia
- Pulm HTN -O2 dependent-
- Osteomyelitis
- Chronic pain
- Poor compliance with HU
- AIHA; Goiter
- 5 – 7 ED visits; 1 - 3 admissions/yr.
- Delay completing Master degree due to illness and cognitive disorder

1 sibling w HgbSβ0thal
2 siblings Hgb AS; No HLA transplant match
Case presentation 1
6 yrs later- Now

30 yo AA F; Hgb SS
Hx:
• CVA w transient hemiparesis -16 yo
• Recurrent ACS/Pneumonia
• Pulm HTN -O₂ dependent
• Osteomyelitis
• AIHA; Goiter
• Chronic pain
• Poor compliance with HU
• 5 – 7 ED visits; 1-3 admissions/yr.
• Delay completing Master degree due to illness and cognitive disorder
1 sibling w HgbSβ⁰thal
2 siblings Hgb AS; No HLA match

36 yo AA F; Hgb SS
Hx:
• CVA w transient hemiparesis
• Recurrent ACS/Pneumonia
• Pulm HTN -O₂ dependent
• Osteomyelitis
• AIHA
• Goiter
• Chronic pain
• Poor compliance with HU
• 4 – 6 ED visits; 1-2 admissions/yr
• Unable to complete Master degree
• Cholecystectomy
• Severe obstructive sleep apnea
• Headache; Chiari I malformation
22yo AA M; Hgb Sβ⁰thal

Hx:
- Priapism during childhood
- Scoliosis
- GERD
- Condyloma
- Smoker
- < 1 ED visits/yr
- No admissions since 10 yo.
- Completed college in NYC
- UNC employee

1 sibling w Hgb SS
2 siblings Hgb AS
Case presentation 2
6 yrs later

23yo AA M; Hgb Sβ0thal
Hx:
  - Priapism during childhood
  - Scoliosis
  - GERD
  - Condyloma
  - Smoker
  - < 1 ED visits/yr;
  - No admissions since 10 yo.
  - Completed college in NYC
  - UNC employee

1 sibling w Hgb SS
2 siblings Hgb AS

29yo AA M; Hgb Sβ0thal
Hx:
  - Priapism
  - Scoliosis
  - GERD
  - Condyloma
  - Smoker
  - 2.2009 Multiple ICH/SAH due to basilar / supraclinoid aneurysms
  - Cortical blindness; Memory loss
  - Unable to tolerate exchange Tx
  - 4.2011 6/6 Allo nonmyeloablative SCT
    - Thrombocytopenia -ITP-
    - Vitreal hemorrhage
    - Headaches
    - Getting independent living & job training
Case presentation 3

45yo AA M; Hgb SC

Hx:
- Bilateral retinopathy and L eye bleed
- R hip and L shoulder AVN;
- S/P R hip replacement 2005
- GERD
- Sleep apnea
- Hypertension
- Diabetes Mellitus
- Employee as office manager. Longer episodes of missing work due to hospitalizations.
- 5 – 7 ED visits; 1-4 admissions/yr

1 sibling w Hgb SC; 1 sibling w Hgb AS
Case presentation 3

6 yrs later

45yo AA M; Hgb SC

Hx:
- Bilateral retinopathy and L eye bleed
- R hip and L shoulder AVN;
- S/P R hip replacement 2005
- GERD
- Sleep apnea
- Diabetes Mellitus
- Employee as office manager. Longer episodes of missing work due to hospitalizations.
- 5 – 7 ED visits; 1-4 admissions/yr

1 sibling w Hgb SC; 1 sibling w Hgb AS

51yo AA M; Hgb SC

Hx:
- Bilateral retinopathy and L eye bleed
- Bilateral hip and L shoulder AVN;
- S/P R hip replacement 2005 / L hip replacement 2008 complicated with hardware infection
- Depression
- GERD
- Sleep apnea
- Hypertension
- Diabetes Mellitus Now insulin dep
- Now on disability due to worsening illness.
- 5 – 8 ED visits; 3-6 admissions/yr
Sickle Cell Syndromes

Sickle Cell Anemia (Hgb SS)

Double -heterozygous states

Sickle $\beta$ thalassemia (Hgb S$\beta^+$ thal & Hgb S$\beta^0$ thal)
SC disease
SD disease

Others Hgb S related hemoglobinopathies

Hgb SO$_{arab}$ SHPFH
Shift

Pediatric

Adult Disease
Age at death for SCD in 1979, 1989, 1999 and 2006

Improvements in SCD Care

- Early case identification by neonatal screening -all 50 states-.
- Prevention of pneumococcal sepsis through prophylactic antibiotics and vaccination.
- Improvement on longevity and QoL by Hydroxyurea therapy
- Primary and secondary stroke prevention
  - 11% of patients with SCD experience at least one clinical stroke episode by the age of 20 years. 24% by age 45.
  - Up to 35% have silent strokes.
Early Mortality in Adults with SCD
Outcome of Sickle Cell Anemia: A 4-Decade Observational Study of 1056 Patients.

Median age of death: 37 years

Causes of Mortality

Mortality in Adults with SCD: Pulmonary Hypertension as a Risk Factor

Gladwin, M et al. *NEJM.* 2004; 26;350(9):886-95
An Endothelial Disease

Factors intrinsic to red blood cells (RBCs)
- Sickle hemoglobin polymerization
- Rheology of sickle RBCs
- Cellular dehydration
- RBC deformability and mechanical fragility

Factors extrinsic to red blood cells
- Whole blood viscosity
- White blood cell factors
- Endothelial factors
- Adhesion of sickle RBCs to endothelium
- Intimal hyperplasia
- Hemostatic factors
- Vascular factors

Hebbel, R et al. Microcirculation 11: 1290151, 2004
The Ages of Sickle Cell Disease

- Childhood - Infections, Strokes
- "Golden Years" - 12-20
- Young Adulthood - 20-40 Acute events
- Older Adulthood - >40 Organ failure/End organ damage
Clinical Manifestations of SCD

Vaso-occlusive = Painful episode/crisis:
Most common episodes, hallmark of the patient with SCD
- Measure of disease severity; correlate with early death in adult patients.
- Predisposing factors: Hypoxia, dehydration, vasospasm, infections, menstruation, acute temperature changes, Acidosis, anxiety/depression and physical exhaustion.

Hemolytic:
- Acute and rapid RBC destruction; Rare frequency
- Clinical findings: malaise, pallor, icterus and jaundice
- Labs: falling Hct and elevated reticulocytes count, LDH and bilirubin. Hemoglobinuria.
- Associated with concurrent G6PD deficiency, sepsis or malaria.
- If chronic: associated with bilirubin stones and biliary obstruction
Clinical Manifestations of SCD

Aplastic:
- Decreased RBC production in the bone marrow added to the usual RBC peripheral destruction.
- Clinical findings: Increased weakness. Falling Hgb and RBC volume with decrease reticulocytes.
- Usually associated with infection - Parvovirus B 19
- Extensive marrow necrosis. May be 2ry to folic acid deficiency

Sequestration:
- Massive pooling of RBC by the spleen or liver with significant fall of Hgb and Hct.
- More frequent in infants and small children
- Clinical findings: Variable symptoms from weakness to shock, abdominal pain, painful splenomegaly.
- Falling Hgb and RBC volume; Thrombocytopenia.
- May occur in adults with splenomegaly (Hgb SC or Sβ+ thal)
Other Clinical Manifestations

Constitutional:

Defective host defenses in sickle cell disease

- Opsonophagocytic defect (altered complement pathway)
- Functional (anatomical asplenia)
- Depressed granulocyte bacterial kill.
- Increase risk for infection
  - Pneumococcus and Salmonella.
- Delayed growth and development
- Absence of splenic function after year 3-4.
## Other Clinical Manifestations

<table>
<thead>
<tr>
<th>Pulmonary/lungs</th>
<th>Cardiac dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Infection</td>
<td>- Ventricular enlargement = compensatory mech of volume overload</td>
</tr>
<tr>
<td>- Fat embolism</td>
<td>- Systolic ejection murmur due to hyperdinamic state</td>
</tr>
<tr>
<td>- Acute chest / ARDS</td>
<td>- Right heart failure due to recurrent pulmonary HTN and infarcts</td>
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<tr>
<td></td>
<td>- Myocarditis associated with iron overload.</td>
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<tr>
<td></td>
<td>- Pericarditis associated with renal failure/sepsis</td>
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<tr>
<td></td>
<td>- Thrombosis</td>
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<tr>
<td></td>
<td>- Pulmonary infarcts</td>
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<td></td>
<td>- Pulmonary Hypertension</td>
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</tbody>
</table>
Other Clinical Manifestations

**Genito-urinary:**
- Functional: papillectomy (isosthenuria and hematuria)
- Glomerulonephritis (tubular Ag, post strep infections)
- Renal tubular dysfunction
- Pyelonephritis (Kidney infections)
- Interstitial nephritis  - Priapism

**Hepatobiliary:**
- Hepatic sequestration
- Biliary tract disease (cholelithiasis, cholecystitis)
- Cirrhosis  - Hepatitis  - Hepatic infarcts

**Musculoskeletal**
- Arthritis - tap joints  - Osteomyelitis (Salmonella, Staph)
- Bony infarcts - fish mouth vertebrae
- Aseptic/Avascular necrosis (any joint)
- Dactylitis (hand- food Syndrome)
Other Clinical Manifestations

Ocular:
- Central retinal artery occlusion
- Retinal arteriolar occlusion
- Neovascularization (Sea fans)
- Retinal detachment/infarcts
- Vitreous hemorrhage
- Anterior chamber ischemia

CNS:
- Cerebral infarcts with increased risk of recurrence (67% in children)
- Subarachnoid and intracerebral hemorrhage
- Fat embolization

Skin
- Legs ulcers
Common Symptoms/Complications

- Anemia
  - Hyperhemolysis
  - Aplastic episodes
  - Acute splenic sequestrations
- Vaso-occlusive Episodes (Tissue damage and Hypoxia)
- Pain syndromes (Bone, joints, muscle, chest)
  - Acute pain episodes
  - Acute multiorgan failure
  - Chronic / Neuropathic pain

Common Symptoms/Complications

- Asthma/Reactive Airway Disease
- Infections: Pneumonia, Osteomyelitis
- Priapism
- Leg Ulcers
- Pulmonary Hypertension
- Kidney and liver Failure
- Transfusion related complications
  - Hyperviscosity
  - Immune hemolysis
  - Transfusional Iron overload
Treatment of Common Symptoms

Anemia

- Determine the patient’s baseline Hgb / Hct / Retic
- Address changes from baseline
  - Increase: Dehydration    Hyperviscosity
  - Decrease: Hemolysis     Aplastic Episode     Bleeding
- Iron therapy only for Iron deficiency (Ferritin and transferin)
- “Aplastic episode is a medical emergency” –Parvo-
- Transfusion:
  - Single or chronic
Treatment of Common Symptoms
Anemia and Pain

- Erythropoietin used in specific situations
  - Inability to transfuse – Poor access, Allo-inmunization
  - Renal Insufficiency - Especially if Low Reticulocyte count and in conjunction with Hydroxyurea –
  - Aplastic episode in conjunction with transfusion support
  - Worsening / severe anemia due to hemolysis or bleeding.

- Pain Management
  - Believe and treat the Pain
    - Narcotics
    - Hydration
    - Adjuvant therapy (NSAIDS, Stress management,
  - Treatment of predisposing cause if known
Treatment of Common Symptoms

Immune system compromise

- Treat infections aggressively with a low threshold for antibiotics
- Flu vaccine yearly
- Pneumonia vaccine Q 5-10 yrs
- Hepatitis B vaccine
- Prophylactic penicillin:
  - Routinely prescribed for children with SCD.
  - Not indicated in adult with SCD.
Treatment of Common Symptoms

Priapism

• Medical emergency
• Hydration
• Ice packs
• Surgical detumescence – Aspiration -
• Transfusion
• Pain control
• Hydroxyurea
• Urology referral
• Casodex
• Viagra
Treatment of Common Symptoms

Lower extremity ulcer

- Rest
- Wet to dry saline dressing
- Antibiotics as necessary
- Unna boot
- Moisturize the skin around the ulcer
- Wound clinic referral
- Skin grafts

Hydroxurea use may be associated with new and worsening painful ulcers
Acute Chest Syndrome (ACS)

1st cause of death in adults with SCD
Clinical diagnosis: Hypoxemia, SOB, chest pain, +/- pulmonary infiltrates-ARDS-.
All patients with chest/lung symptoms must be considered for ACS
Evaluation: Blood gas, Chest X ray, cultures, CBC, type and hold
Administer Oxygen if PO2 < 70 mmHg or O2 sat < 92 % RA.
IV antibiotics (Mycoplasma frequent in children)
VQ scan / EKG / thoracocentesis if clinically indicated
Treatment: Transfusion or exchange transfusion
The Toll of Sickle Cell Disease

Years of pain and suffering
Loss of function of main organs (brain, lungs, liver, kidneys, heart, spleen)
Difficulty in maintaining social functioning
  60% do not enter the work force
  Difficulty in maintaining job
High medical costs-average $26,000/year
Shortened life span
Paradigm

SCD Patient vs. Person with SCD
Health Maintenance and SCD

• Often overlooked in sickle cell patients
• Recommended health screenings as for the general population
  • Gynecologic exam
  • Breast exam / Mammogram
  • Colonoscopy
  • Prostate exam and PSA
  • Yearly and age specific vaccines
    • Flu
    • Pneumonia
    • Hepatitis B
    • Herpes
  • Obesity
  • Screening for:
    • Hypercholesteronemia
    • Depression and other mental illness
    • Pulmonary Hypertension
Women and Pregnancy

**Pregnancy Complications:**
- Worsening Anemia and painful Episodes
- Infection, including urinary tract and lungs
- Gallbladder problems including gallstones
- Heart enlargement and heart failure from anemia
- Miscarriage and spontaneous abortions

**Fetus Complications and increased risks:**
- Intrauterine growth restriction (poor fetal growth)
- Preterm birth (before 37 weeks of pregnancy)
- Low birth-weight (less than 5.5 pounds)
- Stillbirth and newborn death
Women and Pregnancy

Pregnancy Management

• Pregnant women with SCD should be managed by a multidisciplinary team with experience of high risk pregnancies.

• Offered pre-conceptual partner screening and appropriate genetic counseling.

• Painful crises are the most common complication thus each obstetric unit should have a clear management protocol for this and other complications.
APPROACHES TO THERAPY

- Chemical inhibition of hemoglobin S polymerization
  - Hydroxyurea, 5-azacytidine.
- Reduction of the intracellular hemoglobin concentration
  - Mg Clortrimazole
- Gene Therapy
  - Transgenic mice
- Bone Marrow Transplant
Hydroxyurea (HU)

- Only FDA approved drug to treat some of the complications of SCD
- HU reduced by nearly half:
  - Frequency of hospitalizations;
  - Incidence of both first vaso-occlusive crisis (3.0 vs. 1.5 months):
  - Time to the second crisis (8.8 vs. 4.6 months)
- Fewer patients treated with HU had chest syndrome (25 vs. 51); or underwent transfusions (48 vs. 73).

Adult Survival in the Hydroxyurea Era

Long term HU use associated with decreased mortality and increased survival.

HU patients did better despite worse baseline disease.

Effect of HU on Overall Survival

Hydroxyurea (HU)

- Underutilized in adolescents and adults due to both provider and patient concerns

<table>
<thead>
<tr>
<th>HuMA Score meaning</th>
<th>Summed HuMA Score</th>
<th>N (%)</th>
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</thead>
<tbody>
<tr>
<td>100% Adherence</td>
<td>0</td>
<td>15 (16.7)</td>
</tr>
<tr>
<td>Good Adherence</td>
<td>1</td>
<td>34 (37.8)</td>
</tr>
<tr>
<td>Poor Adherence</td>
<td>2</td>
<td>28 (31.1)</td>
</tr>
<tr>
<td>Non Adherence</td>
<td>3 or 4</td>
<td>13 (14.4)</td>
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De Castro, L et al manuscript in preparation
Other therapeutic Interventions

Hydroxyurea (HU):

- Only FDA approved drug to treat some of the complications of SCD
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- Long term HU use associated with decreased mortality and increased survival.
Other Therapeutic Modalities

- Penicillin prophylaxis in children.
- Vaccination: Pneumovax, Menactra, Hepatitis B and H Flu
- Folic Acid
- Iron chelation:
  - For treatment of Iron Overload due to frequent transfusions.
  - Desferrioxamine (Desferal) SQ
  - Deferipone (Exjade) Oral
Stroke prevention:

- Most common indication for chronic transfusion:
  - Primary prevention (STOP trial)
    - ~10% of SS and Sβ0thal children have abnormal TCD findings.
    - Among those with abnormal TCD cannot differentiate who would get a stroke and who would not.
  - 2ry prevention - recurrences -.

- Transfusional iron overload, viral illnesses and alloimmunization remain a major adverse outcome of chronic transfusion.
Other therapeutic modalities

Bone marrow transplant
- Experimental therapy.
- Potential cure
- Mini transplant project: BMT on individuals with HLA matched siblings. Goal of chimerism -trait-. 
- Costly 
- High mortality and procedure associated risks

Gene therapy
- Experimental therapy.
- Potential cure
- Goal: change of genetic makeup.
- Not currently available
Life Expectancy and Quality of Life

Life expectancy remains in the 5th or 6th decade.

- Duke cohort of >400 adult patients, mean age of death <46 yrs – stable over last decade.
- By age 40, 48% of surviving patients have documented irreversible organ damage.
- 37% (38/142) found to have depression, which was associated with higher healthcare utilization.
- Illness chronicity, combined with frequent hospitalizations for pain and other medical management, contribute significantly to impaired psychosocial functioning, altered intra- and interpersonal relationships, and reduced QoL

De Castro et al manuscript in preparation
Adults with SCD: Disease Biology Compounded by Systems of Care and Psychosocial Health

- Access to comprehensive care
- Outpatient vs. inpatient management
- Hydroxyurea Use?

Sickle cell type
- Fetal hemoglobin
- Beta globin haplotype
- Hemolysis & Vasocclusion
- Age related illness

Patients with Worst phenotype

- Chronic pain
- Depression
- Neurocognitive deficits
- Stroke
- Unemployment (80%)
- Sexual Dysfunction

Disease Biology

Psychosocial Health

Systems of Care
What Can we Offer Patients with SCD

- Compassionate, comprehensive medical care
  - Acute and chronic pain management
  - Longitudinal and comprehensive health care and psychosocial support
- Drugs that reduce sickling and complications:
  - Hydroxyurea and Iron Chelation
- Bone marrow transplantation
- Future developments (Basic, clinical and translational research)
  - Gene therapy
  - Combination drug therapy
- Advocacy and Education