Sickle Cell Anemia
A Review - 2012

Malaria

- *Falciparum* malaria kills over 1 million children annually
- Half a billion clinical infections / year
- Hundreds of millions of infections with other malaria species
- Even more cases prior to control measures
- Powerful selective force in the evolution of the human genome
Map of Malaria and Sickle Cell Disease

- Gray areas not affected by falciparum malaria
- Solid Yellow denotes distribution of falciparum malaria
- Lines denote distribution of sickle-cell gene

Falciparum Malaria Parasite Lifecycle

Diagram showing the lifecycle of the Plasmodium falciparum parasite, including stages such as sporozoites, trophozoites, and gametocytes.
Development of the Malaria Parasite

- Merozoite attachment (1)
- Reorientation (2)
- Ring stage (3)
- Mid- and late trophozoite stages (4, 5)
- Cell division in the schizont stage (6)

Malaria Parasite Creates “Knobs” on Red Cell Surface
Survival in Malaria-Infested Areas

- People with normal Hgb (left) are subject to death from malaria.
- People with sickle cell anemia (right) are susceptible to death from complications of the disease.
- People with one Hgb A gene and one Hgb S gene have a greater chance of surviving malaria without the toxic effects of the sickle gene.

African Sickle Hemoglobin Haplotypes
A Fourth Mutation From India

Heredity and Sickle Cell Anemia
An Autosomal Recessive Disorder
Sickle Cell Anemia

Hemoglobin A → Hemoglobin S
via a genetic mutation

Ethnic variation:
African-Americans: 1 in 500
Hispanics: 1 in 36,000
Caucasians: 1 in 58,000
(Greece, Italy, Turkey)

Disease Manifestations

- Vaso-occlusive (pain) crisis
- Dactylitis
- Splenic sequestration
- Aplastic crisis
- Functional asplenia
- Osteomyelitis
- Ocular disease
- Priapism
- Stroke
- Acute chest syndrome
- Gallbladder disease
- Pulmonary hypertension
- Delayed puberty
- Learning difficulties
- Iron overload
- Avascular necrosis of femoral head
Sickle Cell Anemia – Several Different Clinical Phenotypes with Varying Severity

- SS homozygous
- Sβ⁰ thalassemia
- SC disease
- Sβ+ thalassemia

- Other sickling disorders: SD, SO₂₅ Arab
  α thalassemia gene co-inherited - ↓ severity of disease

Type of Sickle Cell Disease Can Determine Severity

- Associated disease processes with each type
- SC disease is milder, has less stroke risk
  BUT more eye disease and more hip necrosis
- Sickle beta(+) thalassemia can be very mild
- Sickle beta(0) thalassemia can be just as severe as SS
- SS with co-inherited alpha thal trait- milder disease, BUT increased hip necrosis
### Which Type Is It?

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle cell anemia</td>
<td>S without microcytosis</td>
</tr>
<tr>
<td>Sickle beta thal(0)</td>
<td>S with microcytosis <strong>AND</strong> increased Hgb A2</td>
</tr>
<tr>
<td>Hgb SC disease</td>
<td>SC</td>
</tr>
<tr>
<td>Sickle beta thal (+)</td>
<td>Sa (a=small amount Hgb A) <strong>PLUS</strong> microcytosis and ↑ A2</td>
</tr>
<tr>
<td>Sickle cell anemia with co-inherited alpha thalassemia trait</td>
<td>S with microcytosis and NO increased Hgb A2</td>
</tr>
</tbody>
</table>

### Pathophysiology of Sickle Cell Disease
Sickle Cell Anemia

- Single base pair mutation results in a single amino acid change.

- Under low oxygen, Hgb S becomes insoluble forming long polymers

- This leads to membrane changes “sickling” and vaso-occlusion

Hemoglobin
Sickle Hemoglobin

Normal mRNA

GUG CAC CUG ACU CCU GAG GAG AAG
val his leu thr pro glu glu lys

Normal protein

Mutant mRNA

GUG CAC CUG ACU CCU GUG GAG AAG
val his leu thr pro val glu lys

Mutant protein

Glutamate (glu), a negatively charged amino acid, is replaced by valine (val), which has no charge.

Deoxyhemoglobin S Polymer Structure

A) Deoxyhemoglobin S 14-stranded polymer (electron micrograph)

B) Paired strands of deoxyhemoglobin S (crystal structure)

C) Hydrophobic pocket for $\beta$ Val

D) Charge and size prevent $6\beta$ Glu from binding.

Wisher, JMB 1975
Ruptured Red Cell With Sickle Hemoglobin Polymers Outside the Cell

Normal Red Cells are Bi-Concave Discs
Red Blood Cells from Sickle Cell Anemia

- Deoxygenation of SS erythrocytes leads to intracellular hemoglobin polymerization, loss of deformability and changes in cell morphology.

Red Blood Cell Characteristics

<table>
<thead>
<tr>
<th>Normal Red Blood Cells</th>
<th>Sickled Red Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexible shape, move easily through small vessels</td>
<td>Rigid, stiff shape</td>
</tr>
<tr>
<td>Lifespan 120 days</td>
<td>Stick to vessel walls</td>
</tr>
<tr>
<td></td>
<td>Lifespan 14 days</td>
</tr>
</tbody>
</table>
Vaso-Occlusive (Pain) Crisis

The Most Common Complication of the Disease

Pain Precipitating Factors

- Infection
- Hypoxemia
- Fatigue
- Dehydration
- Strenuous activity
- Exposure to cold
- Stress
- Menses
- Pregnancy
- Altitude - others?
Vaso-Occlusive Crisis

- **Bone infarction** → severe pain: hands and feet in infants; legs, arms, and low back in older children and adults.

- **Abdominal crisis** – intestines, colon, liver → ileus, abdominal distention, megacolon,
  Common in children

  Rare: liver sequestration (extreme ↑ bili)

Dactylitis in a Child With Sickle Cell Anemia
Treatment of Pain Crisis

- Hydration - oral or IV depending on severity
- Warm packs – Therma-Care
- Analgesics – anti-inflammatory such as ibuprofen or ketorolac (Toradol)
- Narcotics – morphine or hydromorphone (Dilaudid) for acute pain control
- Avoidance of hospitalization with home pain management plan with escalating drug potency

Vaso-Occlusive Disease

- **Renal** – hyposthenuria, inability to concentrate the urine → dehydration, ↑ sickling *Hydrate!* → increase fluid intake in summer months. proteinuria in older children and adults

- **Eye** - sickling and infarction of small retinal vessels → neovascularization, retinal hemorrhage, scarring → retinal detachment. Screen beginning around age 10. Common (up to 30%) in SC disease, 2% in SS
Vaso-Occlusive Disease

- **Spleen** - Splenic infarction and SS patients are essentially asplenic by age 8, functionally so much younger. Susceptible to overwhelming infection. *Immunize*, Use prophylactic penicillin, from age 2 months until 5th birthday
- **Brain** – vessel damage, stroke screening beginning at age 2
- **Lung** – acute chest syndrome, pulmonary hypertension

Acute Chest Syndrome
ACUTE CHEST SYNDROME

- Second most common complication, affects ~30% SCD patients, peak age group 2-4 years higher prevalence in winter

- Main criteria in kids: Fever and infiltrate, especially in upper lobes; SOB, chills and cough. Cough is a late effect (Middle/lower lobe infiltrate in older children and adults)

- All febrile kids with sickle cell disease and respiratory symptoms should have a chest X-ray

- Mortality rate ~2% kids, 4% adults, leading cause of death in SCD

Acute Chest Syndrome
Causes

- Infection
- Fat embolism
- Sickling into the lung vessels
- Atelectasis
- Thromboembolism
Infectious Causes

- *Mycoplasma*
- *Chlamydia* — most common
- *Viral*
- *Staph aureus*
- *Strep pneumoniae*
- *Hemophilus influenzae*
- *Klebsiella pneumoniae*

Treatment of ACS

- In children, infection likely: empiric antibiotics a must
  Cover for: S. pneumo, H. flu, atypicals
- Incentive spirometry every 2 hours
- Careful pain control with Toradol/morphine if necessary (allow max inspiratory effort– don’t overmedicate (sedation), don’t undermedicate (can cause splinting), ibuprofen also for pain if not using Toradol
- Supplemental O2 to keep saturation > 92
- Control fever with acetaminophen
- Careful hydration: avoid pulmonary edema - D5W 1/4 NS
- Consider simple transfusion early, be prepared to move them for higher level of care (exchange transfusion)
- Consider dexamethasone – 0.4 mg/kg q 12 hours x 4 doses (maximum 16 mg/dose)
- Prevention: **Influenza vaccine every year in the fall**
Splenic Sequestration

• 15% of sickle cell patients between 6-36 months (SC, Sβ+ thal > SS, Sβ0 thal in older patients)
• Rapid enlargement of spleen $\Rightarrow$ shock
• Drop in hemoglobin > 2 grams
• Rise in reticulocytes, splenomegaly
• Rapid sequestration vs “slow” (platelets)
• Drop in platelets – IMPORTANT!

Cerebrovascular Disease
Cerebrovascular Disease

- Stroke risk 300 x > than patients without sickle cell disease
- ~ 10% with Hgb SS will have a stroke by age 15 years - 2% of patients with Hgb SC
- ~ 30% of sickle cell anemia patients have “silent” strokes
- Abnormal MRIs in 1/3 of patients by age 15

Cerebrovascular Disease
Risk Factors

- Abnormal transcranial Doppler study
- Increased risk if baseline Hgb low or WBC high
- Higher risk if BP high ( > 113 systolic)
- Higher if patient has moy-a-moya collaterals
- Strokes reduced with chronic exchange transfusion
  - keep % Hgb S < 30
MR Angiogram of New Onset Stroke

MRI of New Onset Stroke
How Do We Screen For Risk?

**Transcranial Doppler**
- Doppler ultrasound beginning at age 2 on all children with sickle cell disease
- Velocity of flow in cerebral vessels in children:
  - normal < 170 cm/sec
- Conditionally abnormal: 170 to 199 cm/sec
- Abnormal = > 200 cm/sec

Management of Abnormal TCD’s and Stroke

- TCD velocity > 200 cm/sec on 2 occasions, 3 weeks apart: packed red cell transfusions

- With both stroke and abnormal TCD velocities, goal is to reduce sickle Hgb concentration to < 30% via partial or double volume exchange transfusion, below which level sickling will not occur.

- RBC Phenotype specific blood: matched for C, E and K antigens, Sickledex (-) units, < 2 weeks old
Sickle Cell Nephropathy

Renal Anatomy
Sickle Cell Nephropathy

- **Hyposthenuria**
- polyuria, nocturia
- Usually irreversible by age 10
- **Hematuria**: microscopic and gross. Cause? papillary necrosis usually mild, self limited

- Renal failure over time associated with progressive proteinuria
- Often present by age 30 progressing to chronic kidney disease and dialysis.
- **Monitor for proteinuria yearly. ACE inhibitor if found**
Sickle Cell Retinopathy

Vessel Proliferation In Retina
Screening and Treatment of Eye Disease

• Begin screening for eye disease around 10 years of age, especially in SC patients
• Exams can be conducted by optometrists with dilation
• If disease found, referral to ophthalmology for treatment
• Photocoagulation of proliferating vessels

Workup of a Febrile Patient

• CBC with differential, retic count, blood culture
• O2 saturation
• Chest X-ray: if tachypneic, low sat, cough, rales or wheezes
• Antipyretic
• Antibiotic while awaiting lab and X-ray
  Ceftriaxone IM or IV if available
• Disposition: lab findings, parental reliability
Management at Various Ages

Newborn Period

- Identified by newborn screening confirm diagnosis by family studies on parents
- Begin prophylactic penicillin at 2 months
- Teach parents the basics of the disease
- How to feel for the spleen
- How to use a thermometer
- Recognizing when the baby needs to be seen: 100.4 or greater or appears ill
At the One Year Visit

- O2 saturation yearly, and any acute visit
- Repeat Hgb evaluation – quantitate Hgb F
- Check to be sure immunizations are up to date
- Any manifestations of disease? Splenic enlargement or dactylitis episodes
- Send to lab for red cell phenotype – type for C, E and Kell blood group antigens, results available for future transfusion needs

Two Year Visit

- Begin screening for CNS disease via TCD
- Repeat Hgb F quantitation
- Immunize with polysaccharide vaccines – Pneumovax-23 and Menactra meningococcal vaccine
- Watch for asthma and treat appropriately (risk factor for acute chest syndrome)
5 and 10 Year Visits

• At 5 years: Begin screening for microalbuminuria

• At 10 years: Start screening for retinopathy

Transfusion

• Preoperative transfusion to Hgb 9-10 gm/dl improves morbidity
• Avoid Hgb > 12 gm/dl (hyperviscosity)
• Sickledex (HbS)-negative blood
• Phenotypically match, at least to C, E, Kell
  – Reduces the rate of alloimmunization
• Leukodepleted blood
• Preferably less than 2 weeks old
## Interventions That Have Reduced Morbidity and Mortality in Sickle Cell Disease

- Newborn Screening for Hemoglobinopathies
- Penicillin Prophylaxis
- Transcranial Doppler Screening for Cerebrovascular Disease
- Hydroxyurea Therapy

### Hydroxyurea

- Hydroxyurea induces bone marrow to increase fetal hemoglobin production which interferes with Hgb S polymerization
- Hydroxyurea causes red blood cells to swell. Red blood cells made in the present of hydroxyurea contain more fluid: sickle Hgb less concentrated in larger cell
- Hydroxyurea is currently being used as an experimental treatment. The drug can cause toxicity in some individuals and must be monitored closely.

- Other effects: ↓ WBC’s, ↓ Platelets
Hydroxyurea

- Recommended for persons with 3 or more pain crises/year OR one acute chest syndrome episode
- Recent guidelines are suggesting its use in infants as young as 9 months of age
- Current study: can hydroxyurea improve the abnormal TCD velocities in patients on chronic transfusion regimens sufficiently that they can stop red cell transfusions?

The Effects of Hydroxyurea Over Time

<table>
<thead>
<tr>
<th>Pre-hydroxyurea</th>
<th>8 weeks</th>
<th>20 weeks</th>
<th>22 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb = 7.7 gm/dL</td>
<td>Hb = 7.9 gm/dL</td>
<td>Hb = 9.6 gm/dL</td>
<td>Hb = 10.0 gm/dL</td>
</tr>
<tr>
<td>MCV = 84 fl</td>
<td>MCV = 96 fl</td>
<td>MCV = 105 fl</td>
<td>MCV = 113 fl</td>
</tr>
<tr>
<td>ANC = 8113</td>
<td>ANC = 3700</td>
<td>ANC = 3200</td>
<td>ANC = 1200</td>
</tr>
<tr>
<td>ARC = 247K</td>
<td>ARC = 203K</td>
<td>ARC = 150K</td>
<td>ARC = 124K</td>
</tr>
<tr>
<td>HU = 600mg</td>
<td>HU = 780 mg</td>
<td>HU = 950 mg</td>
<td>HU = 1040 mg</td>
</tr>
<tr>
<td>20 mg/kg/d</td>
<td>25 mg/kg/d</td>
<td>30 mg/kg/d</td>
<td>27 mg/kg/d</td>
</tr>
</tbody>
</table>
Other Therapies for Sickle Cell Disease

Bone Marrow Transplantation

- Historically reserved for patients < 16 years old
- Had to have severe disease: stroke, recurrent acute chest syndrome, severe pain crises, cerebrovascular disease, recurrent acute chest
- Matched sibling donor needed
- Mortality 5 to 10% historically
New Developments in BMT

- Less toxic conditioning regimens
- Mixed chimerism” both donor and recipient marrow present→ SS disease to AS trait
- Cord blood stem cells: dosage too low for non-myeloablative regimens
- Haploidential transplants: ideal but not yet practical due to lack of prep regimen

Novel Potential Therapies

- Pomalidomide— a derivative of thalidomide
  Similar effect to hydroxyurea:
  Increases Hgb F production AND increases stem cell numbers
- Suppression of BCL11A protein increases fetal Hgb production : knockout of the gene in mice cures sickle cell disease (in mice). How to shut it off in humans?
Gene Therapy

- Proof of concept recently with successful treatment of a Hgb E-β thalassemia patient
- Risk of malignant transformation with random gene insertion using viral vectors
- Need for targeted gene insertion to reduce risk of malignancy and gene transcription must be highly functional for adequate hemoglobin production – high efficiency insertion into stem cells also needed

The End
Sickle Cell Anemia
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