What is Sickle Cell Disease?

- Human adult hemoglobin has 4 proteins, 2 α-globins and 2 β-globins.
- "Sickle" hemoglobin is caused by a genetic mutation in the β-globin gene (chr. 11) that substitutes valine for glutamic acid, changing the shape of β-globin.
- Hemoglobin molecules clump together in long chains, with effect intensified in low-oxygen environments.
- Red blood cells become "sickle" shaped instead of their normal smooth round shape.
- Several other mutations in the β-globin gene that cause milder forms of sickling.

What is Sickle Cell Disease?

- Sickled cells last about 20-30 days in the bloodstream, compared to 120 days for normal red blood cells.
- Sickled cells stick to blood vessel walls, releasing cytokines and other inflammatory markers.
- Sickling causes RBC clumping which impedes blood flow and causes tissue damage.

Genetics and Severity

<table>
<thead>
<tr>
<th>Electrophoretic patterns in common hemoglobinopathies</th>
<th>HbA</th>
<th>HbS</th>
<th>HbC</th>
<th>Hbf</th>
<th>HbA1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>95-100</td>
<td>0</td>
<td>&lt;1</td>
<td>&gt;3.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Beta-thalassemia minor</td>
<td>90-95</td>
<td>0</td>
<td>&lt;1</td>
<td>1-2.5</td>
<td>&gt;3.5</td>
</tr>
<tr>
<td>Sickle-cell trait</td>
<td>91-97</td>
<td>15-35</td>
<td>0</td>
<td>&lt;2</td>
<td>&lt;3.5</td>
</tr>
<tr>
<td>Sickle-beta-thalassemia</td>
<td>5-10</td>
<td>0</td>
<td>35-50</td>
<td>0</td>
<td>2.1-10</td>
</tr>
<tr>
<td>Sickle-beta-thalassemia</td>
<td>0</td>
<td>80-90</td>
<td>0</td>
<td>2.1-10</td>
<td>&gt;3.5</td>
</tr>
<tr>
<td>Sickle-β-β thalassemia</td>
<td>0</td>
<td>40-50</td>
<td>30-40</td>
<td>30</td>
<td>2.1-15</td>
</tr>
</tbody>
</table>

Hb: hemoglobin. *Numbers indicate the percent of total hemoglobin for an untransfused adult patient. β-thalassemia minor, shows HbH (thalassemia), have normal or low HbA levels with markedly increased HbS levels. β-thalassemia major, have a low in HbA1c concurrent with alpha thalassemia.

Common Presenting symptoms

- Early Childhood:
  - Dactylitis
  - Splenomegaly/sequestration
  - Fever/bacteremia
  - Osteomyelitis
- Late childhood/teenage
  - VOC
  - Acute chest
  - Aseptic necrosis
  - Stroke, learning delays
- Adulthood
  - Arterial ulcers
  - Pulmonary infarct/PE
  - Congestive heart failure
  - Nephropathy/Retinopathy
  - Stroke
Acute severe pain associated with sickling and occlusion of blood vessels

Most common complication of sickle cell disease

May present as early as 6 months of age, often with dactylitis

Most common sites of pain are extremities, chest, and back

Most frequent in HbSS and HbSβ0-thalassemia

Individuals with >3 hospitalizations for VOC in a year are at increased risk for early death

Vaso-Occlusive Crisis

Principles and goals of Pain Management in VOC

- Early Communication with Family
- Reassuring Psychotherapy and Oxygen Therapy
- Non-Pharmacological Approaches
- Pain as a Symptom of the Patient
- Habit reversal for chronic pain

Patient Story

http://www.youtube.com/watch?v=JgAVWl5hmE0&list=UUwXpF9cgPmi3MZZwBkBVVzg&index=2&feature=plcp

Accomplishing Pain Control

- Analgesics in the first 45 minutes
- Opioids or non-opioids as needed
- Individualized pain plans
- Pain assay every 30 minutes; consider close escalation by 10% if pain remains uncontrolled

Individualized Pain Plans

- Patient-specific pain management plans designed based on what has worked for that patient in the past
- More rapid decline in pain score
- Decreased re-admission rates
- Decreased admission rates (better home pain management)
- Increased patient satisfaction (less likely to feel they are treated like addicts)

Supportive Care in VOC

- Incentive spirometry and early ambulation important to prevent atelectasis and acute chest syndrome
- Supplemental oxygen for SpO2 < 95%
- Oral antihistamines for opioid-associated itching
- Close monitoring of respiratory status and over-sedation; make sure naloxone ordered with PCA
- Heat packs or lidocaine patches for localized pain
- Consider pain team consult/alternative therapies (massage, relaxation videos, psychiatry)
- Keep in mind other etiologies of pain (pneumonia, acute cholecystitis)
Clinical diagnosis requires BOTH of the following criteria:

- New pulmonary infiltrate on chest radiograph
- One or more of the following:
  - Chest pain
  - Temperature >38.5°C
  - Tachypnea, wheezing, cough or retractions
  - Hypoxemia relative to baseline measurements

Acute Chest Syndrome: Epidemiology

- Major cause of morbidity and mortality in SCD
- 2nd most common cause of hospitalization in SCD (after vasoocclusive pain crisis), and most common cause of death
- Occurs more commonly in winter months
- Peak incidence in children 2-4 years of age
- Can be present on admission or develop as a complication of other sickle cell emergencies

Acute Chest Syndrome: Pathogenesis

- 50% of cases occur during hospitalization for VOC
- Use of opioids may lead to hypoventilation
- VOC localized to rib, spine, or abdomen in particular contributes to hypoventilation
- Recent surgery (post-op atelectasis)
- Asthma

Any patient with VOC pain and shortness of breath or new oxygen requirement needs a chest x-ray to rule out ACS!

Risk Factors

- Adequate pain control
- IV fluids
- Lab evaluation: CBC/diff, reticulocyte count, T&S, blood cultures if patient is febrile
- Maintain O2 sat ≥ 92% (with nasal cannula or BiPap if needed)
- Antibiotics: a third generation cephalosporin like ceftriaxone and a macrolide like azithromycin to cover for atypical organisms (mycoplasma and chlamydia)
- pRBC transfusion if indicated, consider early on in course

Management of ACS

Management of ACS: Indications for transfusion

- Simple transfusion
  - Oxygen saturation <92% in room air
  - Hct 10-20% below patient’s baseline, or dropping Hct during admission
  - Clinical or radiological progression of disease without impending respiratory failure
- Exchange transfusion
  - Progression of illness despite simple transfusion
  - Severe hypoxemia
  - Multi-lobar disease
  - Previous history of ACS or severe cardiopulmonary disease
  - Goal is to reduce HgbS to <30% Hgb should not exceed 10 g/dL
**Stroke**
- 10% of patients with HgbSS will have a stroke in their lifetime
- Etiology: stenosis/occlusion of ICA or MCA
- May be precipitated by ACS, aplastic crisis, or other acute change in Hgb
- Consider possible stroke for new:
  - severe headache
  - seizure
  - altered mental status
  - hemiparesis
  - gait disturbance
  - dysphasia

**Stoke Management**
- Assess ABCs and put patient on cardiac monitor
- Head of bed flat unless contraindicated
- Maintenance IV fluids
- Labs: CMP, Mg, Phos, CBC, Coag panel, type and screen, Hgb electrophoresis and reticuloocyte count
- Strict NPO
- STAT head CT and CTA of head and neck
- IF CT shows subarachnoid or intracerebral hemorrhage >>> consult neurosurgery
- Consider exchange transfusion to decrease HbS <20-30%

**Stroke Prevention**
- Primary Prevention (before a stroke)
  - Transcranial Doppler velocity monitoring yearly
  - If >200, need MRI +/- intervention
  - MRI -> Moya-Moya, need intervention
  - Gold standard: regular simple transfusion
  - Hydroxyurea is just as good (TWITCH trial)
- Secondary Prevention (after a stroke)
  - 60-90% recurrence risk in the first 2 years after stroke
  - Gold standard is regular exchange transfusions
  - Hydroxyurea for pts unable to transfuse (SWITCH)

**Heart Failure and Sickle Cell**
- The heart is at risk in many ways throughout the lifetime of patients with SCD
  - Constant ischemia
  - Reperfusion injury
  - Hemolytic anemia
  - Inhibits NO release 
  - Vasodilation 
  - Increased systemic vascular resistance
  - Increased cardiac output to increase O2 delivery
  - Pulmonary vasculopathy
  - Pulmonary HTN
  - Renal Dysfunction
- Screening:
  - Echo: TRV as surrogate measure for pulmonary HTN
  - Consider for patients with baseline low O2 saturation or resistant HTN

**Is there a Cure?**
- The first "Cure": Hematopoetic stem cell transplant
  - Ablate stem cells using chemotherapy/infus/DN, then transfuse donor stem cells peripherally
  - Best results with matched sibling donor
  - Need 40-50% engraftment for success
  - Lifelong immunosuppression
  - In some ways like trading one chronic disease for another

**Gene Therapy in a Patient with Sickle Cell Disease**
- Gene therapy is more promising; case report published earlier this year in France
- Likely still needs chemotherapy conditioning
- Less side effects after treatment
References


