Sickle Cell Disease
Hematology Fellows Conference
July 16th, 2012
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# Randomized Controlled Trials in Adults with SCD

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multicenter Study of Hydroxyurea in Sickle Cell Anemia</strong>(^{15})</td>
<td>Hydroxyurea reduces the frequency of painful episodes, acute chest syndrome, transfusions, hospitalizations</td>
</tr>
<tr>
<td><strong>Preoperative Transfusion in Sickle Cell Disease</strong>(^{28})</td>
<td>Simple blood transfusion to increase the Hb level to 10 g/dL is as effective as exchange transfusion to reduce Hb S to 30%</td>
</tr>
<tr>
<td><strong>Prophylactic Transfusion in Pregnancy</strong>(^{16})</td>
<td>Prophylactic blood transfusion to increase the Hb level to 10 g/dL compared to transfusion for Hb &lt; 6 g/dL or for emergent indications did not improve obstetrical or perinatal outcomes but reduced the incidence of painful episodes</td>
</tr>
<tr>
<td><strong>Captopril for Albuminuria in Sickle Cell Anemia</strong>(^{33})</td>
<td>Captopril reduces albuminuria in normotensive patients</td>
</tr>
<tr>
<td><em><em>Poloxamer 188</em> for Treatment of Acute Vaso-occlusive Crisis</em>*(^{12})</td>
<td>Poloxamer 188 reduces the duration of acute painful episodes</td>
</tr>
</tbody>
</table>

* Non FDA-approved
Pathophysiology

Intracellular polymer content results in RIGIDITY, changes in cell shape, and membrane distortion.
Complications

1. Pain episodes
2. Strokes
3. Increased infections
4. Leg ulcers
5. Avascular necrosis
6. Hemolysis
7. Early gallstones
8. Pulmonary hypertension
9. Chronic kidney disease
10. Priapism
11. Spleen or liver sequestration
12. Retinopathy
13. Delayed growth
14. Thrombosis

Pain episodes are most common reason for emergency room visits and hospitalizations.
Patient History

• 33 year old with Hgb SS disease
• Presents to clinic for treatment guidance for osteomyelitis of the R tibia with draining non-healing skin ulcer
• Typically 2 crises/year- most tx at home.
• Complications;
  – Multiple episodes of pneumonia
  – Pt reported being heavily alloimmunized with several transfusion reactions. Last transfused in 1998.
Case History

- **Medications:**
  - Hydroxyurea 1500/day
  - Percocet PRN

- **PE: Afebrile**
  - Mid shin deep lesion draining serosanguineous fluid. No erythema around the site.

- **Labs**
  - WBC- 7.75 with ANC of 3000
  - Hgb -10.3 g/dl
  - MCV - 110 fl
  - Plt 446,000 K
  - Indirect Coombs negative
Case History

• Sees Ortho/plastics- will require extensive surgery with skin and muscle flaps.
• What is the current standard of care for a pt with SCD undergoing major surgery?
• If Ms. J. needs blood does the negative indirect Coombs mean it is safe to proceed with transfusion?
Transfusion

- Simple v. Exchange
- Indications
Simple Transfusion in SCD

- Giving several units of blood
- Improve dyspnea
- Severe fatigue
- Heart failure associated with an oxygen-carrying deficit
- Decrease percentage of Hb S containing cells.
Simple Transfusion in SCD

• Risks:
  – Excessive blood viscosity
    • the post-transfusion Hb level should not exceed 10 to 11 g/dL to prevent this
  – Increase stroke risk associated with blood transfusion
    • Limited data – one retrospective study showed an increased risk of hemorrhagic stroke associated with recent (in the prior 14 days) transfusion.
Simple Transfusion in SCD

• Risks:
  – Alloimmunization
    • Occurs in up to 30% of adult patients who receive frequent transfusions;
    • Can cause delayed transfusion reaction or life threatening hyperhemolysis
  – Iron overload
  – Infection
Blood Viscosity and Sickle Cell

• Blood viscosity increases with increasing hemoglobin level.
• Elevated viscosity limits blood flow and oxygen transport.

Poiseuille equation

\[ \text{velocity} = \frac{\pi \cdot p \cdot r^4}{8 \cdot l \cdot \eta \cdot 8} = \pi \cdot (\text{pressure}) \cdot (\text{radius of the tube}) \cdot (\text{length of tube}) \cdot (\text{viscosity}) \]
Blood Viscosity and Sickle Cell

- Blood from a patient with sickle cell anemia has a significantly higher viscosity than normal blood at the same hemoglobin level.
- Deoxygenated sickle blood has 10-fold greater viscosity than oxygenated sickle blood at the same hemoglobin level.
Blood Viscosity and Sickle Cell

• Increased viscosity dramatically promotes the physiology of sickling.
  – Flow will be slowest in vessels of small radius (capillaries, arterioles and venules) and under lower pressures (venules).
Exchange Transfusion and SCD

• Rapidly reduces the concentration of Hb S
• Can be used when simple transfusion would result in hyperviscosity or volume overload.
• Most useful to decrease immediate complications of sickle cell disease.
Exchange Transfusion

• Replacement of sickle cells by normal cells can help prevent further vaso-occlusion,
  – pre-existing vasoocclusion may not be reversed.
• Red cell exchange rapidly decreases rate of hemolysis which decreases
  – liver processing of bilirubin
  – damage to renal tubular cells
  – scavenging of nitric oxide by free hemoglobin released from sickle cells.
Conventional Indications for Transfusion

- **Simple Transfusion**
  - Symptomatic anemia
  - Acute chest syndrome
  - Preparation for major surgery
  - Acute splenic or hepatic sequestration

- **Exchange Transfusion**
  - Acute neurologic event
  - Severe acute chest syndrome
  - Acute multiorgan failure
  - Preparation for major surgery
  - Acute splenic or hepatic sequestration
Transfusion and Surgery

Table 3. Serious or Life-Threatening Complications:*

<table>
<thead>
<tr>
<th>Complication</th>
<th>Group 1 (N=303)</th>
<th>Group 2 (N=301)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of operations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before, during, or after surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscellaneous intraoperative event</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Acute chest syndrome</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Fever or infection</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Miscellaneous postoperative event</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Painful crisis</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Neurologic event</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Renal complication</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Any complication</strong></td>
<td><strong>31</strong></td>
<td><strong>35</strong></td>
</tr>
<tr>
<td>After surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acute chest syndrome</strong></td>
<td><strong>10</strong></td>
<td><strong>10</strong></td>
</tr>
<tr>
<td>Fever or infection</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Miscellaneous postoperative event</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Painful crisis</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Neurologic event</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Renal complication</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Any complication</strong></td>
<td><strong>21</strong></td>
<td><strong>22</strong></td>
</tr>
</tbody>
</table>

*Complications associated with transfusions, which are shown in Table 5, are excluded here. The group numbers refer to operations.
Indirect Coombs

**Indirect Coombs test / Indirect antiglobulin test**

Recipient's serum is obtained, containing antibodies (Ig's).

Donor's blood sample is added to the tube with serum.

Recipient's Ig's that target the donor's red blood cells form antibody-antigen complexes.

Anti-human Ig's (Coombs antibodies) are added to the solution.

Agglutination of red blood cells occurs, because human Ig's are attached to red blood cells.
Hemolytic Transfusion Reactions

• Antibody develops to antigen on surface of transfused red cells.
• Occurs in 5-36% of patients with SCD
• Delayed type transfusion reaction (DTHR)
  – Occurs 5- 20 days after transfusion and is caused by antibodies that are not detectable at the time of cross match.
  – Patient will hemolyze transfused cells.
Alloimmunization

- DTHR/ Hyperhemolysis Syndrome
  - If complicated by bystander hemolysis patients break down own cells
  - Characterized by:
    - Severe anemia post transfusion
    - Hgb below pretransfusion level
    - Reticulocytopenia
  - Development of RBC autoantibodies

- Stop transfusions- use IVIG and steroids
Transfusion Pitfalls

• Avoiding delayed transfusion reactions:
  – Ask patient if they were told about antibody or if there was ever a delay in getting them blood products
  – Give every patient phenotypically matched red cells (assuming you have a phenotype)
    • matched blood for at least the C, E, and Kell antigens
    • If a pt has not been transfused in 3 months make sure that blood bank gets/has a phenotype prior to transfusion.
Transfusion Pitfalls: Key Point

• Uncomplicated VOC not indication for transfusion
  – No data that transfusion decreases length of crises.
• No Hgb threshold where transfusion is indicated
  – Pt’s in crises often will have decrease in Hgb below baseline this is not an indication to transfuse
  • If pt has adequate reticulocyte response and is not SOB would not transfuse
Hydration Hazards

• 38 yr old with SS disease. Does not have frequent crises.
• Major complication of SCD is leg ulcers
• Presents with typical VOC secondary to strep. pharyngitis
• Treated with PCA for pain control, antibiotics and NS at 200 cc/hr.
Hydration Hazards

- 24 hrs later on rounds see that nurse has been increasing oxygen to keep pulse ox >95%.
- Pt is on 5L by NC and pulse ox is 94% and c/o CP.
- CXR shows some vascular congestion, no infiltrate
- Over next few hours increasing oxygen demand and Temp of 39°C
- Repeat CXR now with multilobar infiltrates
- Pt is put on 100% NRB
Acute Chest Syndrome

- The most common pulmonary complication
- Leading cause of death in patients with sickle cell disease.
- Clinical diagnosis defined as:
  - Consolidation on CXR
  - Fever
  - Chest pain
Acute Chest Syndrome

Vicious cycle

Pulmonary event

Hypoxia

Sludge in microvasculature

Irreversibly sickled RBC

Impaired hypoxic pulmonary vasoconstriction

Loss of peripheral vasoconstriction

Increased hemolysis
ACS

• Atelectasis
  – Painful rib and vertebral infarctions,

• Pulmonary infection
  – Chlamydia/mycoplasma

• Macro and microvascular infarction

• Fat Embolism

• Pulmonary Edema
Hydration Hazards

- Labs: hgb 7gm/dl (baseline 8gm/dl)
  - Retic 6%
- Chest CT shows bilateral infiltrates
- Pt gets exchanged
- Why did pt develop ACS and why did he get so sick?
  - Might have been infectious...
### Table 3. Overall Predictors of Prolonged Hospitalization, Respiratory Failure, and Neurologic Complications among Patients with the Acute Chest Syndrome. *

<table>
<thead>
<tr>
<th></th>
<th>Percent Requiring Mechanical Ventilation</th>
<th>Odds Ratio (95% CI)$</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory failure‡</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of cardiac disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>12</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>44</td>
<td>6.7 (2.1–22.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>No. of lobes involved on radiographic examination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to 1</td>
<td>3</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>2 to 3</td>
<td>11</td>
<td>2.2 (1.0–4.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>≥4</td>
<td>54</td>
<td>9.0 (2.5–32.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelet count at diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to 199,000/mm³</td>
<td>23</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>200,000 to 399,000/mm³</td>
<td>11</td>
<td>0.9 (0.37–2.1)</td>
<td>0.75</td>
</tr>
<tr>
<td>≥400,000/mm³</td>
<td>8</td>
<td>0.3 (0.10–0.96)</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Acute Chest Syndrome

- Consider transfusion if at risk for respiratory failure:
  - Adults
  - History of cardiac disease
  - Anemia or thrombocytopenia
  - Multilobar pneumonia.
Hydration Hazards

- Echo done following day shows EF of 55%, dilated R and L atria
- RVSP 65 mmHg with TR jet of 3.1 cm/sec
- Patient is diagnosed with Pulmonary hypertension

Hydration led to vascular congestion that ultimately led to acute chest syndrome
Pulmonary Hypertension

- 30% of screened adult with SCA (PAP ≥ 30 mm Hg).
- Autopsy studies- 75% of sickle cell patients have histological evidence of PHTN at time of death.
- Insidious onset in most patients.
Diagnosis

- The velocity of regurgitant blood across the tricuspid valve during systole
  - Dx can be made non-invasively with echo
- PHTN defined by a specific TRV $\geq 2.5$ m/sec
- Moderate-to-severe PHTN defined by a TRV $\geq 3.0$ m/sec
- Multiple studies show that TRV $\geq 2.5$ m/sec in SCD is associated with 50% 2 yr. mortality.
Survival Curve By TR Jet Velocity

N Engl J Med 2004;350:886-95
Is this True PHTN?

• Bachir in France prospective multicenter study.
  – 403 consecutive adult patients with SCD had echo.
  – TRV of more than 2.5 m/s in 96 patients.
  – Right heart catheterization- normal pulmonary artery pressure in 72.
  – Echo falsely positive in 75% of cases.
  – True pulmonary artery hypertension rare- affecting 1.6%.

*Blood. 2010;116(5):687-692*
If most of these patients don’t have true PHTN, why are they dying?

N Engl J Med 2004;350:886-95
Avoiding Hydration Hazards

• Recognizing the prevalence of disease
• Echo defined PHTN is a bad prognostic sign
  – Patients are likely more at risk for volume overload with aggressive hydration
  – Pulmonary pressures are known to increase with VOC and especially ACS.
• Frequent evaluations of volume status.
• Patients need pulse ox on presentation and at regular intervals.
• Send type and screen (be prepared)
Preventing Crises: The Hemoglobin Switch

Just before birth there is a switch from γ-globin to β-globin expression.
Effects of HbF in SS disease

- **Pain**:  
  - Hb F <= 9%  
  - Hb F > 9%  

- **Chest**  
  - Hb F <= 9%  
  - Hb F > 9%  

- **Ulcer**  
  - Hb F <= 9%  
  - Hb F > 9%  

- **Death**  
  - Hb F <= 9%  
  - Hb F > 9%  

References:  
- Platt, 1991  
- Castro, 1994  
- Koshy, 1989  
- Platt, 1994
How Does HbF Prevent Complications

- HbF reduces Hgb S concentration
- Hb F cannot enter the deoxy sickle hgb polymer
- Switch from hbF to hbS is reversible
Phase II Trial of Hydroxyurea in SS Disease Increases Hb F
Multicenter Study of Hydroxyurea

- Double-blind, randomized
- Pt’s with SS or Sβ0thalassemia
- 299 patients with history of 3 or more crises/year
- Decrease in number of crises/yr (2.5 v. 4.5 p < 0.001)
- Decrease in ACS (25 v. 51 p < 0.001)
- Decrease in no. of patients undergoing transfusion (48 v. 73 (p= 0.001)
Hydroxyurea Benefits not Limited to Hb F Induction

- Improved erythrocyte morphology and deformability
- Lowering of circulating leukocyte and reticulocyte counts,
- Reduction in hemolysis
- Local release of nitric oxide

Current Opinion in Hematology
Issue: Volume 18(3), May 2011, p 158–165
### Table 1. Study Outcomes for Adults Receiving Hydroxyurea for Sickle Cell Disease

<table>
<thead>
<tr>
<th>Clinical outcomes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain crises</td>
<td>Decrease (high-grade evidence)</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>Decrease (high-grade evidence)</td>
</tr>
<tr>
<td>Blood transfusion therapy</td>
<td>Decrease (high-grade evidence)</td>
</tr>
<tr>
<td>The acute chest syndrome</td>
<td>Decrease (high-grade evidence)</td>
</tr>
<tr>
<td>Priapism</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Stroke</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Leg ulcer</td>
<td>Not significantly different</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Prevention of end-organ damage</td>
<td></td>
</tr>
<tr>
<td>Spleen</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Kidney</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Brain (cerebral blood flow)</td>
<td>Being evaluated</td>
</tr>
<tr>
<td>Mortality</td>
<td>Decrease (low-grade evidence)</td>
</tr>
</tbody>
</table>
Probability of 10-year overall survival in SCD HU v No HU

No patients developed malignancy
Treat with Hydroxyurea

• In adults with sickle cell anemia
  – who have 3 or more SCD-associated moderate to severe pain events in a 12 month period
  – who have SCD-associated pain that interferes with daily activities and quality of life
  – with a history of severe and/or recurrent acute chest syndrome
  – who have severe symptomatic chronic anemia that interferes with daily activities or quality of life
Starting Hydroxyurea

• Counsel patient regarding need for contraception and careful follow up
  – Male patients consider sperm cryopreservation
• Starting dosage (500 mg capsules): 15 mg/kg/day [5-10 mg/kg/day if renal or hepatic dysfunction]
• Monitor CBC every 2 weeks
  – Maintain absolute neutrophil count ≥ 2,500/uL
  – Maintain platelets ≥ 95,000/uL
Hydroxyurea Management

- Escalate daily dose 500 - 1000 mg every 6-8 weeks [maximum: 35 mg/kg/day if no evidence of toxicity].
  - Most studies done with titration to MTD to see effect
- Once desired effect is achieved blood counts can be monitored every 4-8 weeks
Common Mistakes with Hydroxyurea

• Not initiating therapy in eligible patients
  – hgb F levels are high
  – Patient concerns over toxicity

• Failing to titrate dose to MTD
  – Most studies with HU – dose titrated to MTD
Common Mistakes with HU

• Too short a trial of drug
  – Patients/providers should anticipate that it will take 3-6 months to see an effect
  – Patients need to be reminded to be adherent

• Stopping HU during hospital admission
  – Only stop if counts are too low
Pain Management

- Narcotics
- Synergistic agents (NSAIDS)
- Local measures (warmth)
- Coping skills
- Hydration
Case Presentation

27 yr old male with Hgb SS disease

Labs 12/02
- WBC-8.8#/cu mm
- Hgb- 10.8 g/dl
- HCT- 29%
- Plt- 286 K/Cu MM
- Retic 7.6%/ abs 229.8

Labs 8/25/03
- WBC- 4.6#/cu mm
- Hgb 10.3 g/dl
- HCT 28%
- Plat 364 K/ Cu MM
- Retic 7.5%/Abs 210.1
“As previously stated, he refused any substance abuse counseling, denying any such problem. He was therefore discharged to take folate and Tylenol. On further presentations to the Johns Hopkins Emergency Room, he should be evaluated carefully given his history of drug-seeking behavior and suspected narcotic addiction. In particular, **he should not be given narcotics, be put on the sickle cell pathway, or dispensed any prescriptions for narcotics unless there is objective evidence of a vasoocclusive crisis.**”
What Is the Best Way to Treat the Pain?

• Benjamin et al.
  – Bronx Comprehensive Sickle Cell Center.
  – Used a specific assessment and treatment protocol in the setting of a day hospital,
    • pain was controlled in 90% of patients,
    • hospital admissions decreased by 40%
    • average length of stay for hospitalized patients decreased by 1.5 days.
  – Key- patients were assessed and started on treatment within 15-20 minutes of arrival
  – Patients were assessed at half hour intervals for pain, psychological distress, pain relief and adverse events.
What Is the Best Way to Treat the Pain?

• Montañez et al.
  – Clinical pathway, inner city hospital in Chicago.
  – Five basic features:
    • Tolerant patients were identified so that they would not be inadequately treated
    • Patient controlled analgesia
    • Meperidine was not used
    • Acetaminophen and ibuprofen were used for drug synergy
    • Patients were promptly converted to equivalent oral doses of narcotics.
  – Patients achieved pain relief 80% faster
  – Decrease in LOS of 50%
Overall Statistics for the SCIC

- On average 50% JHH ED visits ended with pt admitted.
- From 2/08-4/10:
  - 2023 visits
- Average visits/day = 3.7 (range 0-10)
- Average visits/day 2010 = 4.49 (1-9)
- Overall 80% of patients are discharged home. Since 1/2009 90% discharged home.
- Over two years 36% of patients had single visit
- Median number of visits per patient was 3
Pain in SCD

• 232 patients age 16 years or older with sickle cell disease.
• Daily diary for up to 6 months
• Pain reported on 54.5% of 31,017 analyzed patient-days
• 29.3% of patients reported pain in greater than 95% of diary days
• Only 14.2% reported pain in 5% or fewer diary days
• Crises without utilization were reported on 12.7% of days and utilization on only 3.5%

Figure. Breakdown of diary days.

<table>
<thead>
<tr>
<th>Days</th>
<th>Mean Pain Intensity (±SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utilization (with or without crisis)</td>
<td>5.9 ± 0.1</td>
</tr>
<tr>
<td>Crisis (without utilization)</td>
<td>5.0 ± 0.1</td>
</tr>
<tr>
<td>Pain (without crisis or utilization)</td>
<td>3.9 ± 0.1</td>
</tr>
<tr>
<td>No pain</td>
<td>0.0 ± 0.0</td>
</tr>
</tbody>
</table>
Coping Skills
Conclusions

• Many of the mistakes made are in complications seen mostly in adults where there is less data about management.

Key points:
– Don’t transfuse for asymptomatic anemia
– Think about end-organ damage
– Remember patients with SCD live with pain everyday, reward patients for having good coping skills!