Disclosure

- Consultant: TerumoBCT
Organizing Committee

• Ravi Sarode, M.D. Committee Chair
• Bruce Sachais, M.D.
• Samir Ballas, M.D.
• Eileen Gavin Karr, RN
• Alicia Garcia, RN
• Haewon Kim, M.D.
• Karen King, M.D.
• Lance Williams, M.D.
Presenters

- Martin Steinberg, M.D.
  - Pathophysiology of Sickle Cell Disease
- Keith Quirolo, M.D.
  - Acute Chest Syndrome
- Michael DeBaun, M.D.
  - Cerebrovascular Accidents
- Mark Gladwin, M.D.
  - Pulmonary Hypertension
Presenters

- Haewon Kim, M.D.
  - Red Cell Exchange Procedure
- Araba Afenyi-Annan, M.D.
  - Selection of Red Cells
- Cathy Hulitt, RN
  - Technical and Nursing Aspects
Martin Steinberg M.D.

- Pathophysiology
- Vasoocclusion and hemolysis
- Complications
- Transfusion
  - Indication
  - Methods
  - Complications
Pathophysiology
Polymerization

- β6 Triplet codon
- GAG → β6 Glu → Valine residue
- HbS solution
- HbS polymer
- Oxygenated → Deoxygenated
- HbS cell
- Cell heterogeneity

EC, ISC, RBC, R
Red Cell Membrane
Hemolysis: Nitric Oxide
Pathophysiology
Hemolysis--Adhesion

Hemolysis, endothelial dysfunction

Viscosity, vaso-occlusion

Precapillary arteriole
Smooth-muscle cells
Capillary
Postcapillary venule

Endothelial cells
Erythrocyte
Monocyte
Platelets

NO
Arg
O2

ET-1
Hb

NOS
XO

Decreased NO bioactivity
Pulmonary hypertension
Leg ulceration
Priapism
Stroke

Increased vaso-occlusion
Pain crisis
Acute chest syndrome
Osteonecrosis
### Complications of Sickle Cell Disease

<table>
<thead>
<tr>
<th>Complications</th>
<th>Further Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Chest Syndrome</td>
<td>Sickle Renal Disease</td>
</tr>
<tr>
<td>Asthma (60% of Children)</td>
<td>Renal Failure</td>
</tr>
<tr>
<td>Obstructive Restrictive Lung Disease</td>
<td>Osteonecrosis of bone</td>
</tr>
<tr>
<td>Pulmonary Hypertension</td>
<td>Retinopathy/Optic arterial occlusion</td>
</tr>
<tr>
<td>Cerebral Vascular Disease</td>
<td>Priapism</td>
</tr>
<tr>
<td>Stroke (Silent and Completed)</td>
<td>Acute and Chronic Pain</td>
</tr>
<tr>
<td>Pregnancy (High Risk of Morbidity)</td>
<td>Life expectancy: approximate 40 years</td>
</tr>
<tr>
<td>Red Cell Transfusion Complications</td>
<td></td>
</tr>
<tr>
<td>Iron Overload</td>
<td>Alloimmunization/Hyperhemolysis</td>
</tr>
</tbody>
</table>
Indications for Transfusion

**Acute Transfusion**
- Surgery (simple to Hgb 10g/dl)
- Acute Chest Syndrome*
- Clinical Stroke*
- Severe Anemia (simple)
  - Splenic Sequestration
  - Parvoviral infection
- Multiorgan Failure*
  - Hyperhemolysis (caution)

**Chronic Transfusion**
- Abnormal TCD*
- Silent Infarct*
- Stroke*
- Severe Disease*
  - Recurrent ACS
  - HU failure with complication
- Pain* (questionable)
- Organ Transplantation*

*Indication for Red Cell Exchange
Summary

- Vasoocclusion and hemolytic anemia cardinal features of sickle cell disease
- Both simple and exchange transfusion have a role in treatment
- No randomized trials supporting exchange or simple transfusion
- High hemoglobin (SC, SS alpha thalassemia) dictates exchange transfusion
- Exchange can reduce iron exposure, can more accurately predict post-transfusion hemoglobin S and hematocrit
• Acute Chest Syndrome
  • Etiology
    • Pulmonary Hypertension
    • Interstitial Lung Disease
  • Diagnosis
    • ACS differential:
      • Pulmonary Thrombotic Embolus
      • Fat embolus
      • Infarct
  • Treatment
    • Simple Transfusion
      • Role
      • Chronic transfusion for ACS
    • Red Cell Exchange
      • Treatment goals, Variables affecting treatment
## ASFA Recommendations

### Sickle Cell Disease: Acute

<table>
<thead>
<tr>
<th>Condition</th>
<th>Procedure</th>
<th>Recommendation</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Stroke</td>
<td>RBC EX</td>
<td>Grade 1C</td>
<td>I</td>
</tr>
<tr>
<td><strong>Acute Chest Syndrome</strong></td>
<td>RBC EX</td>
<td>Grade 1C</td>
<td>II</td>
</tr>
<tr>
<td>Priapism</td>
<td>RBC EX</td>
<td>Grade 2 C</td>
<td>III</td>
</tr>
<tr>
<td>Multiorgan Failure</td>
<td>RBC EX</td>
<td>Grade 2C</td>
<td>III</td>
</tr>
<tr>
<td>Splenic/Hepatic Sequestration</td>
<td>RBC EX</td>
<td>Grade 2C</td>
<td>III</td>
</tr>
<tr>
<td>Intrahepatic Cholestasis</td>
<td>RBC EX</td>
<td>Grade 2C</td>
<td>III</td>
</tr>
</tbody>
</table>

### 2014 NHLBI Evidence-Based Recommendations for Managing Acute Complications of SCD

#### Acute Chest Syndrome

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibiotics, O2 sat&gt;95%, monitoring</strong></td>
<td>Strong Recommendation, Low</td>
</tr>
<tr>
<td><strong>Simple transfusion if Hgb &gt; 1.0 g/dl below baseline, Hgb &gt; 9.0 g/dl elective transfusion</strong></td>
<td>Weak Recommendation, Low</td>
</tr>
<tr>
<td><strong>SC, SB(^+) Thalassemia, Hematology consult for transfusion</strong></td>
<td>Strong Recommendation, Low</td>
</tr>
<tr>
<td><strong>Exchange Transfusion for Oxygen Saturation &lt; 90% on supplemental oxygen, progressive infiltrate, decreasing Hgb</strong></td>
<td>Strong Recommendation, Low</td>
</tr>
<tr>
<td><strong>Incentive spirometry</strong></td>
<td>Strong Recommendation, Moderate</td>
</tr>
</tbody>
</table>

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Caveats

- Published Literature primarily pediatric
- Studies are Retrospective
- There are no Prospective Randomized Trials for:
  - Blood transfusion as treatment of acute chest syndrome either simple or exchange
  - Comparing simple with exchange transfusion
Definition

- Various definitions have been used
- New pulmonary infiltrate
  - One consolidated segment (not atelectasis)
- Chest pain
- Temperature of > 38.5°C
- Tachypnea
- Wheezing or cough

Acute Chest Syndrome

- Second second most common diagnosis for hospitalization
- 25% of deaths in sickle cell disease
  - Leading single cause of death

<table>
<thead>
<tr>
<th></th>
<th>Vichinsky 1997</th>
<th>Vichinsky 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Death Rate</td>
<td>1.8%</td>
<td>3%</td>
</tr>
<tr>
<td>Children 0-9 years</td>
<td>--</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Children Overall</td>
<td>1.1%</td>
<td>2%</td>
</tr>
<tr>
<td>Adults</td>
<td>4.1%</td>
<td>9%</td>
</tr>
</tbody>
</table>

- Risk factor for stroke
# Presentation

<table>
<thead>
<tr>
<th>Complaint/Symptom</th>
<th>Percent With Complaint/Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Children</td>
</tr>
<tr>
<td>Admission ACS</td>
<td>61%</td>
</tr>
<tr>
<td>Fever</td>
<td>86% (90.6%)</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>27% (5.5%)</td>
</tr>
<tr>
<td>SOB</td>
<td>31% (17%)</td>
</tr>
<tr>
<td>Extremity Pain</td>
<td>22%</td>
</tr>
<tr>
<td>Rib Pain</td>
<td>14% (23%)</td>
</tr>
</tbody>
</table>

Pulmonary Emboli

- Discharge Database Review: 5 years
  - 2001 to 2006

- Rate African American (0.59%) = SCD (0.58%)
- CT scan African American (46%) = SCD (42%)
- Mortality SCD without PE: 1.4%, with PE: 6.2%

★ No difference in genotype (SS, SC, SB thal)
★ No clinical features to distinguish PE

Pulmonary Thrombosis ACS

- 125 patient screened with CT
- 144 episodes of ACS
- 20 Positive

Prevalence 17%

- Only Predictors
  - Thrombocytosis (P= 0.048)
  - Bilirubin (P=0.048)

- DVT not increased in SCD versus AA with PE

Low percent of main or lobar thrombosis

- May indicate a local process
- In this study vessels < 1 mm could not be visualized

Fat Emboli Syndrome

- Marrow necrosis
- Fat embolization
- Release of free fatty acids
- Lung injury
- Hypoxia VQ mismatch
- Increased hemoglobin polymerization

Fat Emboli Syndrome

• Increased frequency in patients with high hemoglobin: SC, SS with α-thalassemia trait, other variants. Fetal hemoglobin not protective

• 81% had respiratory failure, 83% neurologic event

• 50% of cases were diagnosed with FES at autopsy

★ Mortality overall: 64%
  • 29% Exchange transfusion: mortality 29%
  • 31% received simple transfusion: mortality 61%
  • 38% received no transfusion: mortality 91%

Simple versus Exchange Pediatrics

- Retrospective study of 81 patients with ACS
  - Simple transfusion (ST): n = 51
  - Red Cell Exchange (RCE): n = 15
  - ST + RCE: n = 15

- Clinical Respiratory Score for all patients
  - 6 variables scored 0 through 2
    - Respiratory rate, Auscultation, Accessory muscles, Mental status, O2 saturation, Skin color

<table>
<thead>
<tr>
<th></th>
<th>ST (n=51)</th>
<th>U-RCX (n=15)</th>
<th>ST+RCX (n=15)</th>
<th>Overall P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRS at Dx</strong></td>
<td>3.0 ± 2.0</td>
<td>4.7 ± 2.0</td>
<td>3.8 ± 2.5</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>CRS after ST</strong></td>
<td>2.0 ± 1.6</td>
<td>-</td>
<td>4.9 ± 1.9</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>CRS after RCE</strong></td>
<td>-</td>
<td>2.4 ± 1.2</td>
<td>2.1 ± 1.6</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>HGB at Dx</strong></td>
<td>7.3 ± 1.4</td>
<td>8.0 ± 1.7</td>
<td>7.6 ± 1.6</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>HGB after ST</strong></td>
<td>10.2 ± 1.2</td>
<td>-</td>
<td>9.5 ± 2.2</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>HGB after RCE</strong></td>
<td>-</td>
<td>10.4 ± 1.1</td>
<td>10.3 ± 1.1</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>O2 sat at Dx</strong></td>
<td>92.3 ± 7.6</td>
<td>87.0 ± 9.5</td>
<td>89.5 ± 10.4</td>
<td>0.90</td>
</tr>
<tr>
<td><strong>Days on O2</strong></td>
<td>2.4 ± 2.3</td>
<td>3.7 ± 2.1</td>
<td>4.7 ± 1.8</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Pre RCX % S</strong></td>
<td>-</td>
<td>71.6 ± 14.9</td>
<td>49.2 ± 13.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Post RCX %S</strong></td>
<td>-</td>
<td>19.5 ± 7.9</td>
<td>17.3 ± 9.7</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>LOS (days)</strong></td>
<td>5.5 ± 3.9</td>
<td>5.7 ± 2.7</td>
<td>6.5 ± 2.7</td>
<td>0.59</td>
</tr>
</tbody>
</table>

**CSR** = Clinical Respiratory Score
## Exchange versus Simple Adults

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exchange (n=20)</th>
<th>Simple (n=20)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>31.4</td>
<td>30.3</td>
<td>0.74</td>
</tr>
<tr>
<td>Genotype</td>
<td>18 SS, 2 SB⁰</td>
<td>19SS, 1 SB⁰</td>
<td>0.33</td>
</tr>
<tr>
<td>Prior ACS (%)</td>
<td>70</td>
<td>90</td>
<td>0.16</td>
</tr>
<tr>
<td>HU on admission (%)</td>
<td>40</td>
<td>45</td>
<td>0.75</td>
</tr>
<tr>
<td>Bronchodilator (%)</td>
<td>75</td>
<td>65</td>
<td>0.49</td>
</tr>
<tr>
<td>PAP &gt; 25 mmHg (%)</td>
<td>10</td>
<td>17</td>
<td>0.67</td>
</tr>
<tr>
<td>LDH Peak</td>
<td>1171</td>
<td>688</td>
<td></td>
</tr>
<tr>
<td>LDH median</td>
<td>725</td>
<td>641</td>
<td>0.08</td>
</tr>
</tbody>
</table>

### Post Exchange: Outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exchange (n=20)</th>
<th>Simple (n=20)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS post procedure</td>
<td>5.6</td>
<td>5.9</td>
<td>0.82</td>
</tr>
<tr>
<td>LOS hospital</td>
<td>8.4</td>
<td>8.0</td>
<td>0.76</td>
</tr>
<tr>
<td>RBC Transfused (Units)</td>
<td>10.3</td>
<td>2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admit Hgb (g/dl)</td>
<td>8.6</td>
<td>7.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Pre-TX (g/dl)</td>
<td>8.0</td>
<td>6.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Peak Hgb (g/dl)</td>
<td>10.4</td>
<td>9.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>DC Hgb (g/dl)</td>
<td>9.6</td>
<td>8.7</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Did not report the percent hemoglobin S
Summary

- Presentation difference between adults and children with ACS
- Fluid overload/hyperviscosity can lead to leukoencephalopathy
- Pulmonary Hypertension is not a risk factor for ACS
- Pulmonary fat emboli have a poor prognosis without exchange transfusion
- Pulmonary emboli is not increased in ACS, pulmonary thrombosis is more common
- Exchange transfusion shown effective in pediatrics, not in adults: little data and no prospective studies
• Primary Stroke Prevention
• Secondary Stroke Prevention
• Exchange as primary therapy after primary stroke
• Transfusion for silent stroke
Historical Epidemiology

Diagram showing the hazard function for hemorrhagic stroke and infarctive stroke over age (yr).
Modified with TCD/Transfusion
Transfusion: Acute Stroke

- Restore blood flow
- Maximize tissue oxygenation
- Reverse ischemia
- Prevent further ischemia

Transfusion methods
  - Simple transfusion
  - Exchange transfusion
Post Transfusion

- Hemoglobin 10-12 g/dl
- Hemoglobin S < 30% (>viscosity)
  ★ Recommend < 15% (opinion)
- As soon as possible to reverse ischemia
Viscosity Following Transfusion

Oxygen transport declined as the hematocrit and viscosity increased.
Optimal hematocrit between 27 and 33%
Decrease in oxygen transport hematocrit >35%

Anemia and increased percent hemoglobin S increased cerebral blood flow
Increased cerebral blood flow is associated with stroke risk

Fluid Balance/Hypertension

- Five pediatric patients age 3 to 9 with ACS
- Required ventilation support
- All had a positive net fluid balance
- All had hypertension for age at some time during hospitalization
- All developed Posterior Leukoencephalopathy

Secondary Prevention

- Chronic blood transfusion
  - Simple transfusion
  - Exchange transfusion
- Stem cell transplant
- Hydroxyurea
- Revascularization Procedures
Retrospective Review

- 137 Patients from 14 centers transfused for at least five years
- Two groups
  - Group I had an antecedent event (26)
  - Group II no antecedent event (111)
- Rate of stroke after two years was higher in Group II (1.9/100 patient years)
  - 31 patients in this group had second strokes
- In Group I there were no additional strokes
- Percent hemoglobin S after 3 years could be > 30% in some centers (9/14)

Second Stroke

- Overall
  - 23% of patients had second stroke
  - 31 of 137 mean time to second stroke 4.0 years
  - Event rate was 2.2/100 patient years: 23%
  - 11 of 31 had 2 or more recurrences: 35%

- First two years
  - Group I: 11.5% (3 of 26)
  - Group II: 7.2% (8 of 111)

- After 2 years
  - Group I no events over next 10 years
  - Group II 20 events: 19% (1.9/100 patient years)

- Patients had percent hemoglobin S < 30% in most cases of second stroke
Silent Cerebral Infarct
Impact of SCI on SCD

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study</th>
<th>SCD without SCI</th>
<th>SCD with SCI</th>
<th>MD [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armstrong et al 1996</td>
<td>1</td>
<td>90 105 17.42</td>
<td>82.8 21 13.29</td>
<td>-7.20 [-13.79; -0.61]</td>
</tr>
<tr>
<td>Steen et al 1998</td>
<td>2</td>
<td>78.9 12 8.9</td>
<td>70.6 10 12.1</td>
<td>-8.30 [-17.33; 0.73]</td>
</tr>
<tr>
<td>Watkins et al 1998</td>
<td>3</td>
<td>86.03 30 12</td>
<td>79 4 5.7</td>
<td>-7.03 [-14.08; 0.02]</td>
</tr>
<tr>
<td>Beräudin et al 2000</td>
<td>4</td>
<td>86.6 104 17.1</td>
<td>82.6 17 15.7</td>
<td>-4.00 [-12.15; 4.15]</td>
</tr>
<tr>
<td>Brown et al 2000</td>
<td>5</td>
<td>81.67 30 16.68</td>
<td>81.91 11 14.43</td>
<td>0.24 [-10.17; 10.65]</td>
</tr>
<tr>
<td>Wang et al 2001</td>
<td>6</td>
<td>84.8 122 13.5</td>
<td>77.2 43 13.7</td>
<td>-7.60 [-12.34; -2.86]</td>
</tr>
<tr>
<td>Thompson et al 2003</td>
<td>7</td>
<td>90.2 93 13.1</td>
<td>86 20 12.8</td>
<td>-5.29 [-10.50; 0.10]</td>
</tr>
<tr>
<td>Kra et al 2006</td>
<td>8</td>
<td>87.59 22 11.42</td>
<td>90.6 5 3.05</td>
<td>3.01 [-2.46; 8.48]</td>
</tr>
<tr>
<td>Hijnans et al 2011</td>
<td>9</td>
<td>80 9 9</td>
<td>79 12 14.4</td>
<td>-1.00 [-11.05; 9.05]</td>
</tr>
<tr>
<td>SITT</td>
<td>10</td>
<td>99.63 51 13.08</td>
<td>92.94 171 12.5</td>
<td>-6.59 [-10.64; -2.54]</td>
</tr>
</tbody>
</table>

Overall Effect (MD) [95% CI]: -4.76 [-7.20; -2.33]
Test for Overall Effect: \( z = -3.83 \) (\( p < .001 \))
Test of Heterogeneity: \( q = 12.88, \) df = 9 (\( p = .17 \))

Hemoglobin and blood pressure increase risk of SCI
CVD Risk

Abnormal TCD
Cumulative risk of abnl TCD by 14 yrs: 29.6%

Stenosis
Cumulative risk stenosis by 14 years: 22.6%

Silent infarct
Cumulative risk silent Infarct by 14 years: 28.2%

Overall risk
Cumulative risk CVD by 14 years: 49.9%

Summary

• Completed Stroke: **No** transfusion
  • 60 to 80% chance of recurrence in three years

• Completed Stroke: Transfusion
  • 45% probability for second stroke in five years

• Silent Infarct: **No** Transfusion
  • 22% probability for second infarct or enlargement in five years

• Silent Infarct: Transfusion
  • 10% probability for second infarct or enlargement in five years

• Red cell exchange superior to simple transfusion initially and chronically
Mark Gladwin, M.D.

- Hemolysis and vascular damage
- How much free hemoglobin impairs NO signaling
- Clinical relevance of hemolysis
- Role of transfusion therapy in treatment of pulmonary hypertension
Hemolysis, endothelial dysfunction

Precapillary arteriole
Smooth-muscle cells
Capillary
Endothelial cells
Erythrocyte

Decreased NO bioactivity
Pulmonary hypertension
Leg ulceration
Priapism
Stroke

Vascular Constriction
Pulmonary and Systemic hypertension
Erectile Dysfunction
Dyspepsia
Abdominal Pain
NO Consumption is high in SCD
BP with Hemoglobin Infusion

- Ringers infusion
- Hemoglobin infusion
- Stop hemoglobin infusion
Heme concentration MAP

% increase in MAP vs Time (s)

% increase in MAP vs Estimated heme conc (μM)
TRV Estimation of PHT

Tricuspid Regurgentent Velocity: Indirect measure of pulmonary hypertension

NIH TRV Clinical Correlation

• Correlated with:
  • Markers of hemolysis ★
    • Increased bilirubin, LDH, Low hemoglobin
  • Systemic Hypertension, renal dysfunction, and leg ulcers

• Not correlated with:
  • Leukocyte count, platelet count, Fetal hemoglobin
  • Pain episodes or acute chest syndrome
Summary

- Hemolysis leading to NO depletion is a major contributor to morbidity
- Pulmonary hypertension is a risk factor for mortality in SCD
  - At least 10% of patients at risk
- There are no trials or retrospective data on transfusion therapy for pulmonary hypertension treatment
Haewon Kim, M.D.

- Endpoint targets after exchange
- Adjusted for iron overload
- Exchange for small children
- Isovolumetric Hemodilution (IHD)
  - Advantages and disadvantages
  - Benefits
  - Should IHD become standard for chronic transfusion
  - Contraindications for IHD
Overt Stroke

• Using same literature Dr. Kim agrees with Dr. DeBaun that exchange is preferred for both the initial treatment and chronic treatment of overt stroke in sickle cell disease.
## Target Levels

<table>
<thead>
<tr>
<th>Target</th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post Hct/Hbg</td>
<td>27-30%/9-10 g/dl</td>
<td>30%-35% (&lt;36%)*</td>
</tr>
<tr>
<td>Post Hgb S</td>
<td>&lt; 30%</td>
<td>30-50%</td>
</tr>
<tr>
<td>FCR</td>
<td>25-30%</td>
<td>40-60%</td>
</tr>
<tr>
<td>Fluid Balance</td>
<td>100%</td>
<td>100-110%</td>
</tr>
</tbody>
</table>

*Target Hemoglobin Hematocrit can be adjusted for severe iron overload:*

- Hct/Hgb: 27% (9.0 g/dl) ⭐
- Maintain Hgb S << than 50%

  (EDITORIAL: S should be ≤ 30% if possible)
Erythrocytapheresis

• Acute
  • Rapid and accurate reduction in percent hemoglobin S without fluid overload.

• Chronic
  • Less iron exposure
  • Possible to reverse iron overload
Challenges of Exchange

- Expense and reimbursement ★
- Increased blood exposure
  - Decreased alloimmunization
  - Increased potential for infectious disease
- Availability (due to reimbursement ★)

Possible Positive Effects:
- Thrombocytopenia
- Possible effect of plasma removal (cytokines)
Isovolumetric Hemodilution

- Initial Reduction in Hematocrit with normal saline
- Followed by red cell exchange
- The higher the initial hematocrit and the lower the reduction the more blood product is saved
# IHD-RBCx Contraindication

<table>
<thead>
<tr>
<th>Type of RBCx</th>
<th>Chronic</th>
<th>Episodic: Non-acute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Condition</td>
<td>STABLE (Editorial: what is “Stable”)</td>
<td></td>
</tr>
<tr>
<td>Neurologic Exam</td>
<td>≥20 kg</td>
<td>≥30 kg</td>
</tr>
<tr>
<td>TCD, MRI/MRA</td>
<td>≥27%</td>
<td>≥30%</td>
</tr>
<tr>
<td>Min Weight (Kg)</td>
<td>≥27%</td>
<td>≥30%</td>
</tr>
<tr>
<td>Min Pre-Hct (S&lt;30%)</td>
<td>≥24%</td>
<td>NA</td>
</tr>
<tr>
<td>Min Pre-Hct (S&lt;50%)</td>
<td>≥21%</td>
<td>NA</td>
</tr>
<tr>
<td>Intra-Hct (S&lt;30%)</td>
<td>≥27%</td>
<td>NA</td>
</tr>
<tr>
<td>Intra-Hct (S&lt;50%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Not Indicated for Acute Red Cell Exchange
IHD-RBCx

- Decreased exposure
  - Increased efficiency of exchange
  - Prolong transfusion interval
  - Cost reduction due to less blood use

- Consider IHD-RBCx as standard if chronic transfusions considered
Iatrogenic Anemia

- Series of studies (11) at UCSF by Weiscoff et. al. with isovolumetric hemodilution in young healthy subjects.

- Reduction of hematocrit to 15%, (hemoglobin 5 g/dl) caused memory deficits, decreased reaction time, fatigue, and vital sign changes

- Rapidly reversed with autologous transfusion

- Could be reversed with oxygen administration

- Safe hemoglobin in young normal individuals is thought to be 7 g/dl
Acute Anemia

• Chronic and acute reduced hemoglobin a risk factor for cerebral vascular insult in SCD (parvoviral infection/sequestration)

★ Very low hemoglobin (2 to 6 g/dl) increased stroke risk by 58 times

• Anemia is a stroke risk for children with and without sickle cell disease
  ★ Hemoglobin < 5.5 g/dl increases risk

Think Twice

- Before stating IHD-RBCx: there must be confidence that the patient can tolerate the low hemoglobin without compromise: that they are stable neurologically without MRI/MRA changes and have minimal risk of stroke.
Araba Afenyi-Annan, M.D.

- Selection of Red Cells for transfusion in sickle cell disease
- Evidence for using phenotypic RBC’s
- If a partial match: honor which antigens
- Cost benefit ratio for using phenotypic RBC’s
Alloimmunization

- General population <5% to 12%
- Sickle cell disease 25% to >30%
  - Difficulty matching blood in emergency
  - Largest users of the rare blood registry: 20-30%
- Autoantibody formation
  - Associated with blood exposure
  - About 8% of patients
Delayed Hemolytic Transfusion Reactions

• Previous exposure to antigen occurs in one to three weeks, may be asymptomatic or mistaken for pain episode.

• Hyperhemolysis
  • Bystander hemolysis of patients own cells
  • Life-threatening anemia worse with transfusion
  • Etiology may not be apparent
Published Recommendations

- NIH Manual ("Redbook")
  - Recommended phenotypically matched blood
    - C,E,Kell and use of sickle dex negative blood
- NHLBI Recommendations
  - C,E,Kell with moderate recommendation and low quality evidence.
- GAPS Recommendation published in AJH
  - Recommended that this is an area for research
Evidence for Phenotyping

- Vichinsky 1990
  - 30% sickle cell patients alloimmunized versus 5% of controls

- Rosse 1990 Cooperative Study
  - 18.6% alloimmunization rate without phenotyping

- Vichinsky 2001 STOP Study
  - 0.3% per unit
Alloimmunization

- Alloimmunization study (Cox, 1988)
  - Rate of alloimmunization was 30%
- Cooperative study (Rosse, 1990)
  - Rate of alloimmunization was 15.6%
- Transfusion study (Vichinsky, 1995)
  - Rate of alloimmunization was ~7%
    - 10% aggressively; 5% straight transfused
- Acute chest study (Vichinsky, 2000)
  - Rate of alloimmunization was 1%
Recommendations

• NHLBI recommends C, E, Kell phenotyping with moderate recommendation and low quality evidence.

• Generally recommended by sickle cell physicians, supported by numerous studies
# Common Antibodies

<table>
<thead>
<tr>
<th>Antibody</th>
<th>N</th>
<th>% Sensitized</th>
<th>% Transfused</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-C</td>
<td>102</td>
<td>30.2</td>
<td>5.6</td>
</tr>
<tr>
<td>Anti-E</td>
<td>143</td>
<td>42.3</td>
<td>7.9</td>
</tr>
<tr>
<td>Anti-K</td>
<td>95</td>
<td>28.1</td>
<td>5.2</td>
</tr>
<tr>
<td>Anti--Fya</td>
<td>62</td>
<td>18.3</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Rosse, WF et al. Blood. 1990; 76(7) 1431-1437

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Caucasian</th>
<th>African American</th>
</tr>
</thead>
<tbody>
<tr>
<td>U (neg)</td>
<td>0</td>
<td>1/250</td>
</tr>
<tr>
<td>Js(b) (neg)</td>
<td>0</td>
<td>1/319</td>
</tr>
<tr>
<td>Cr(a) (neg)</td>
<td>0</td>
<td>1/6429</td>
</tr>
<tr>
<td>At (a) (neg)</td>
<td>0</td>
<td>1/16,400</td>
</tr>
</tbody>
</table>

ARC Mid-Atlantic Region 2002
Partial Phenotyping

• C,c,E,e,Kell should be honored initially.
• Antibodies may not be persistent so transfusion records should be honored
• As fully as possible phenotype if there is alloimmunization.
• African American donors are more likely to have an antigen negative profile
Cost Effectiveness

- Direct Costs of phenotyping
- Indirect Costs of alloimmunization
  - Extended phenotyping or genotyping
  - Expense of rare antigen negative units
  - Increased morbidity and prolonged hospitalization
- Cost to patient of multiple antibodies
  - Stress and anxiety when transfusion required
- Societal Costs of providing care
- Ethical issues of not providing best practice care due to reimbursement
Unintended Consequences

- African Americans are more likely to have:
  - Trait for hemoglobinopathies
    - Hemoglobins: C, D, Other hemoglobins
  - G6PD deficiency
  - Unusual Rh combinations leading to Rh alloimmunization

Summary

• Use of partly phenotypically matched units recommended
• Use of fully phenotypically matched units if alloimmunized
• Cost should not be a factor given morbidity of not using phenotypic red cells
Cathy Hulitt, RN

- Vascular access for exchange
- Anticoagulation for access
- Sedation in children
- Nursing care
Peripheral & Lines

- Peripheral Lines
  - Adults 40%
  - Pediatrics 20%
  - In both pediatric and adults 40%

- Central Lines
  - Implantable ports 70%
  - Flexible lines 30%
Peripheral Access

- Draw lines can be as small as 20 g
- Return lines can also be 20g
- Emergent use
  - Central Access
- Access is difficult
  - Absent veins, dehydration, weight gain, thrombosis and scaring of veins
Central Lines

- Double lumen
  - 7 to 13 French
  - Short term emergent use: non-tunnled
  - Chronic use: tunneled catheter
- Advantage: easy access, no needles
- Disadvantage: Infection, home care needed
Implantable Ports

- **Vortex**
  - 7.5, 9.6, 11.4 French
  - Single and double lumen

- **Chronic access**

- **Advantage**
  - No home care, less risk of infection

- **Disadvantage**
  - Thrombosis
  - Location may cause access to be difficult
  - Frequent use by hospital staff in admitted
Anticoagulation

- Flushing after use with NS
- Heparin 1000 to 5000 units per ml
- Citrate
- Positive pressure clamp
- TPA
# Guidelines for Access

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Acute Access</th>
<th>Chronic Access</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-15</td>
<td>7 Fr</td>
<td>Medcomp</td>
</tr>
<tr>
<td>16-20</td>
<td>7 Fr</td>
<td>Vortex</td>
</tr>
<tr>
<td>21-30</td>
<td>9 Fr</td>
<td>7.5 SL</td>
</tr>
<tr>
<td>31-40</td>
<td>9 Fr</td>
<td>7.5 SL/DL</td>
</tr>
<tr>
<td>41-50</td>
<td>11 Fr</td>
<td>11.4 DL/SL</td>
</tr>
<tr>
<td>&gt;50</td>
<td>11 Fr</td>
<td>11.4 DL/SL</td>
</tr>
</tbody>
</table>
Nursing

- Knowledge of procedures
  - Competence testing and evaluation
- Knowledge of Side Effects
  - Citrate Reactions
  - Volume status and calculations
  - Transfusion Reactions
- Patient Education