Pediatric Red Cell Exchange
Indications, Benefits, Barriers
View from California
Saturday May 9th
ASFA 2015
## Recommendations for Red Cell Exchange

<table>
<thead>
<tr>
<th>Indication</th>
<th>Procedure</th>
<th>Recommendation</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Babesiosis (severe)</td>
<td>RBC EX (acute)</td>
<td>1C</td>
<td>I</td>
</tr>
<tr>
<td>Babesiosis (Risk)</td>
<td>RBC EX (acute)</td>
<td>2C</td>
<td>II</td>
</tr>
<tr>
<td>Malaria (severe)</td>
<td>RBC EX (acute)</td>
<td>2B</td>
<td>II</td>
</tr>
<tr>
<td>BMT minor ABO Missmatch</td>
<td>RBC EX (Non-Acute)</td>
<td>2C</td>
<td>III</td>
</tr>
<tr>
<td>Polycythemia Vera</td>
<td>RBC EX (acute/NA)</td>
<td>1B</td>
<td>I</td>
</tr>
<tr>
<td>Erythrocytosis</td>
<td>RBC EX (acute/NA)</td>
<td>1C</td>
<td>III</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>RBC EX (NA)</td>
<td>1B</td>
<td>I</td>
</tr>
<tr>
<td>Overdose*</td>
<td>RBC EX</td>
<td>-</td>
<td>III</td>
</tr>
<tr>
<td>CO Poisoning*</td>
<td>RBC EX</td>
<td>-</td>
<td>III</td>
</tr>
<tr>
<td>ABNL Hemoglobin*</td>
<td>RBC EX</td>
<td>-</td>
<td>III</td>
</tr>
</tbody>
</table>

*No category  (From Kim 2014)
2014 Evidence-Based Report

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

<table>
<thead>
<tr>
<th>Acute Chest Syndrome</th>
<th>Strong Recommendation</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics, O2 sat&gt;95%, monitoring</td>
<td></td>
<td>Low</td>
</tr>
</tbody>
</table>

| Simple transfusion if Hgb > 1.0 g/dl below baseline, Hgb > 9.0 g/dl elective transfusion | Weak Recommendation   | Low                 |

| SC, SB+ Thalassemia, Hematology consult for transfusion                             | Strong Recommendation  | Low                 |

| Exchange Transfusion for Oxygen Saturation < 90% on supplemental oxygen, progressive infiltrate, decreasing Hgb | Strong Recommendation  | Low                 |

| Incentive spirometry                                                               | Strong Recommendation  | Quality of evidence |

## Recommendations
### Acute Transfusion

<table>
<thead>
<tr>
<th>Condition</th>
<th>Procedure</th>
<th>Recommendation</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Stroke</strong></td>
<td>RBC EX</td>
<td>Grade 1C</td>
<td>I</td>
</tr>
<tr>
<td>Acute Chest Syndrome</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></td>
<td>III</td>
</tr>
<tr>
<td>Multiorgan/Hyperhemolysis*</td>
<td>RBC EX + PLX</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* No category
### Recommendations

**Chronic Transfusion**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Procedure</th>
<th>Recommendation</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke Prophylaxis/Iron Overload Prevention</td>
<td>RBC EX</td>
<td>Grade 1C</td>
<td>II</td>
</tr>
<tr>
<td>Vaso-occlusive Event</td>
<td>RBC EX</td>
<td>Grade 2C</td>
<td>III</td>
</tr>
<tr>
<td>Pre-Operative</td>
<td>RBC EX</td>
<td>Grade 2A</td>
<td>III</td>
</tr>
<tr>
<td>Completed stroke</td>
<td></td>
<td>No Recommendation</td>
<td></td>
</tr>
<tr>
<td>Hydroxyurea Failure with life-threatening event</td>
<td></td>
<td>No Recommendation</td>
<td></td>
</tr>
</tbody>
</table>

**No Category I indication for chronic transfusion**
Indications for Transfusion
In Sickle Cell Disease

Acute Transfusion
- Surgery
- Acute Chest Syndrome*
- Clinical Stroke*
- Severe Anemia
  - Splenic Sequestration
  - Parvoviral infection
- Multiorgan Failure*
  - Hyperhemolysis

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

*Indication for Red Cell Exchange
Acute Chest
Pediatric Acute Chest Syndrome

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

• Clinical Respiratory Score for all patients
  – 6 variables scored 0 through 2 (max score = 12)
    • Respiratory rate, Auscultation, Accessory muscles, Mental status, O2 saturation, Skin color

# Acute Chest Syndrome

## Laboratory and Clinical Data: Simple (ST), U-RCX, ST+RCE

<table>
<thead>
<tr>
<th></th>
<th>ST (n=51)</th>
<th>U-RCX (n=15)</th>
<th>ST+RCE (n=15)</th>
<th>Overall P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS at Dx</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>CRS after ST</td>
<td>2.0 ± 1.6</td>
<td>4.9 ± 1.9</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>CRS after RCE</td>
<td>-</td>
<td>2.4 ± 1.2</td>
<td>2.1 ± 1.6</td>
<td>0.60</td>
</tr>
<tr>
<td>HGB at Dx</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>HGB after ST</td>
<td>10.2 ± 1.2</td>
<td>-</td>
<td>9.5 ± 2.2</td>
<td>0.13</td>
</tr>
<tr>
<td>HGB after RCE</td>
<td>-</td>
<td>10.4 ± 1.1</td>
<td>10.3 ± 1.1</td>
<td>0.85</td>
</tr>
<tr>
<td>O2 sat at Dx</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>Days on O2</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>Pre RCX % S</td>
<td>-</td>
<td>71.6 ± 14.9</td>
<td>49.2 ± 13.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Post RCX %S</td>
<td>-</td>
<td>19.5 ± 7.9</td>
<td>17.3 ± 9.7</td>
<td>0.49</td>
</tr>
<tr>
<td>LOS (days)</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>
Cerebral Vascular Disease

Stroke
Proposed Pathology of Stroke

Stroke: Exchange Vs. Simple

- Retrospective study N=137
- 5 years of transfusion therapy
- Mean age at stroke: 6.3 years
- Mean follow up 10.1 years
- 31 had recurrent stroke (23%)
  - 57% with simple transfusion
  - 21% with exchange transfusion

<table>
<thead>
<tr>
<th>Initial Treatment of stroke: Time to treatment</th>
<th>Duration of Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; one day (n=52)</td>
</tr>
<tr>
<td>No Transfusion</td>
<td>0</td>
</tr>
<tr>
<td>Simple Transfusion</td>
<td>14 (27%)</td>
</tr>
<tr>
<td>Exchange Transfusion</td>
<td>38 (73%)</td>
</tr>
</tbody>
</table>
Stroke Risk
Chronic Red Cell Transfusion
Cerebral Vessels
Transcranial Doppler

- Illustrates the TCD making the diagnosis of cerebral arterial stenosis: right middle cerebral artery.
- Velocity in an area of stenosis may actually be normal or decreased.
# STOP I

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (130)</th>
<th>Transfusion (63)</th>
<th>Standard (67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow up (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2550</td>
<td>1321</td>
<td>1229</td>
</tr>
<tr>
<td>Median</td>
<td>21.1</td>
<td>22.2</td>
<td>18.3</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>19.6 ± 6.5</td>
<td>21.0 ± 5.7</td>
<td>18.3 ± 7.0</td>
</tr>
<tr>
<td>Strokes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infarct</td>
<td>12</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Intracranial Hemorrhage</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

STOP I Results

- Transfused patients were transfused with partially phenotypically matched red cells (C, E, Kell) every four weeks to maintain a hemoglobin S of 30% or less.
Risk for Silent Infarct

- 189 Stroke Free Patients
- Followed with MRI-MRA
- About 10 years (2.2 to 19.9 years)
- SCI risk was 39.1%
- Baseline hemoglobin of < 7 g/dl < 3 years
  - Hazard Ratio 2.97 (1.43-6/17)
- Acute Anemia and eICR stenosis are risk factors

Anemia and SCI

- baseline Hb
  - ≥ 7g/dL
  - < 7g/dL

Number at risk:
- Group: ≥ 7g/dL
  - 147
  - 146
  - 135
  - 101
  - 73
  - 51
  - 35
  - 24
  - 16
  - 6

- Group: < 7g/dL
  - 24
  - 24
  - 20
  - 13
  - 7
  - 6
  - 5
  - 3
  - 0
  - 0

Log Rank p = 0.002
Hemodynamic Etiology of Stroke

• Baseline cerebral blood flow is determined by age and by degree of anemia
  – Decreased with age, increased with anemia
  – Maximum blood flow velocity between 5-9 yrs.

• Maximum 200 ml/100g/min: level reached in steady state in children with SCA
  – Vasodilation is not possible in children with anemia

• Increased oxygen extraction is the only other method of increasing oxygenation in tissue

Baseline Cerebral Blood Flow
Cerebral Vessel Reactivity in SCD
Cerebral Vascular Disease

• Bernaudin 2011
  – 132 patients, 66 with CVD (50%)
    • 17 isolated abnormal TCD
      – Normalization on transfusion: no stroke
      – Not normal on transfusion: worse CVD
    • 21 isolated silent stroke
    • 28 with mixed findings

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%
Therapy for Stroke Risk

• 109 patients: intensive therapy (82.5%)
  – Chronic transfusion 86 (65%)
    • VOC-ACS, Abnl TCD, Sequestration
  – Hydroxyurea 54 (41%)
    • VOE-ACS, Anemia, Switch from transfusion to HU for abnormal TCD
  – Transplant 26 (19.6%)
    • 25 of 26 engrafted
    • Cerebral vascular disease, VOE, ACS
Scope

• Stroke Risk in Sickle Cell Anemia
  – ~50% of all patients with sickle cell disease will have either:
    • Stroke Risk
    • Ischemic brain injury: Occult Stroke
    • Cerebral vascular disease

• Two thirds or more patients will be treated with transfusion for life
Benefits of Red Cell Exchange
Benefits

• Fluid Balance
• Reduction of inflammatory mediators
• Iron Reduction
• Decreased Alloimmunization
• Improved Outcomes
Transfusion Rheology

- 15 subjects acute single transfusion with a hemoglobin S of > 50%
- Oxygen transport declined as the hematocrit and viscosity increased.
- Optimal hematocrit between 27 and 33%
- Decrease in oxygen transport hematocrit >35%

Fluid Balance

- 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

Inflammatory Mediator Reduction

Small Pediatric Study with only 8 patients and 9 episodes of acute chest syndrome
All admitted for acute chest syndrome
All required oxygen, one ventilated
All received red cell exchange
All recovered
Controls were 6 patients who were well at a clinic visit

<table>
<thead>
<tr>
<th>Inflammatory Mediators Pre- and Post-Exchange Transfusion</th>
<th>Baseline</th>
<th>Post RBC Ex</th>
<th>24 hr Post</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>sVCAM</td>
<td>693 ± 262</td>
<td>-188 ± 173</td>
<td>+213 ± 222</td>
<td>1043 ± 439</td>
</tr>
<tr>
<td>WBC</td>
<td>24.6 ± 8.7</td>
<td>-12.3 ± 8.3</td>
<td>+2.2 ± 3.0</td>
<td>10.8 ± 2.8</td>
</tr>
<tr>
<td>ANC</td>
<td>18.9 ± 8.2</td>
<td>-10.5 ± 7.8</td>
<td>+1.8 ± 2.1</td>
<td>5.3 ± 1.9</td>
</tr>
<tr>
<td>Platelets</td>
<td>388 ± 155</td>
<td>-274 ± 114</td>
<td>+79 ± 41</td>
<td>363 ± 73</td>
</tr>
</tbody>
</table>

Reduced Alloimmunization

Alloimmunization simple transfusion compared to red cell exchange

45 Chronically transfused patients
23 Simple Transfusion
22 Exchange Transfusion
10,949 units transfused

<table>
<thead>
<tr>
<th>Regimen</th>
<th>New Antibody (%)</th>
<th>Total Units Transfused</th>
<th>Total Antibodies</th>
<th>Antibodies/100 units</th>
<th>Alloantibody/100 units</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC EX (22)</td>
<td>3 (13)</td>
<td>7447</td>
<td>3 (1 allo)</td>
<td>0.040</td>
<td>0.013</td>
</tr>
<tr>
<td>Simple (23)</td>
<td>4 (18)</td>
<td>3502</td>
<td>6 (5 allo)</td>
<td>0.171</td>
<td>0.143</td>
</tr>
<tr>
<td>p Value</td>
<td></td>
<td></td>
<td></td>
<td>0.04</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Wahl SK, Garcia A, Hagar W, Gildengorin G, Quirolo K, Vichinsky E. Lower alloimmunization rates in pediatric sickle cell patients on chronic erythrocytapheresis compared to chronic simple transfusions. Transfusion 2012;52:2671-6
IRON
Iron Reduction

• No pathway to remove iron from body
• Each year of simple transfusion adds 12 times more iron than can be recycled or removed
• Daily chelation needed have negative iron balance
Serious Toxicity of Iron Overload

Clinical sequelae of iron overload

- Pituitary: impaired growth, infertility
- Thyroid: hypoparathyroidism
- Heart: cardiomyopathy, cardiac failure
- Liver: hepatic cirrhosis
- Pancreas: diabetes mellitus
- Gonads: hypogonadism
Iron Reduction Without Chelation

12 year old developed elevated transaminases while on chelation with oral chelator. Transfusion for cerebral vascular disease without infarct.
Hematocrit Pre and Post Exchange

Hematocrit %

Time Months

= ~ 27% hematocrit
Hemoglobin S%

S %

Time Months

= ~ 30% S
25 years of red cell exchange now 28 years old

normal range
Hematocrit

![Hematocrit Chart]

- **Hematocrit %**
- **Time Months**
Percent Hemoglobin S

Time Months
Percent Sickle Hemoglobin

Started Red Cell Exchange
Barriers

• Technology
  – Expensive Medical Device and Disposables
  – Trained nurses and physicians
  – Hospital Infrastructure

• Reimbursement
  – Inadequate Reimbursement for therapy

• Venous Access

• Patient Acceptance
Reimbursement

REIMBURSEMENT FOR APHERESIS

Reimbursement: $80.00 per treatment in California

HIDDEN COST: CHELATION

Oral Chelator (pediatric):
– Per Month $5,415
– Annual Cost to State:
  $64,980.00 (small child)
  $110,000.00 (School age)

Injectable Chelator
– Per month $6,680.00

• Annual Cost to State: $80,160.00
Cost: Monitoring Iron Overload

- SQUID  $6,762.00 annually
- Echocardiogram $1,468.00
- Holter monitoring: $1,059.00
- Cardiac MRI: $1,620.00 (reading only)
- Minimal outpatient charges annually are $10,909.00
Laboratory Costs

• Routine
  • Ferritin
  • Liver Function

• Annual or Biannual for Severe Overload
  • Glucose tolerance testing
  • Thyroid function
  • Bone density
  • Ovarian testing in women
Total Costs: California

• Simple Transfusion: with Chelation
  • Red Cell Transfusion $39,898
  • Chelation $110,980 (average adolescent)
  • Monitoring $10,000 +
  – Total Cost: $160,878.00
  • Hospitalization for chelation (> $1000.00/day)

• Red Cell Exchange Total Cost Annually Without Chelation

• Total Cost: $72,096.00
Access