Sickle Cell Disease: To Exchange or Not to Exchange in the Setting of Acute Stroke

Andrew Jones, MD
April 2018
Objectives

• Review and apply the ASFA criteria for red cell exchange (RBCX) in acute stroke sickle cell patients.

• Discuss blood bank methods for rapid diagnosis of sickle cell disease.

• Discuss role of TPA and RBCX in the management of acute stroke, and optimal timing for RBCX.

• Explore calculation of replacement volumes in morbidly obese RBCX patients.
34 year old African American woman
Riding a bus with sudden left eye vision loss
History of HbSS Disease

- HbSS disease
  - Multiple prior crises
  - Avascular necrosis of bilateral hips (date unknown)
  - Several episodes of acute chest syndrome, requiring intubation
  - Prior transient L eye vision loss (4y ago)
  - Frequent pain crises

- Status post cavernous carotid fistula coiling
Additional History

- Morbidly obese (BMI: 50.9 kg/m²)
- Recently moved from out of state to Sacramento, has not established care
- Last RBCX 1y ago
Next Steps?

- Admission and evaluation by neurology
- Imaging (MRI preferred)
- Maintain $O_2$ above 95%
- IV NS at 1-1.5x maintenance rate
- Simple transfusion to raise Hgb to 10 g/dL
- Monitor blood pressure
- Evaluation for other causes (pneumonia, meningitis, sepsis, etc)

Uptodate. “Acute stroke in sickle cell disease.” Mar 2018
Home medications

- Hydroxyurea
- Folate
Allergies

- Toradol (hives)
- Tramadol (hives)
- Morphine (hives)
Physical Exam

• Courtesy of Neurology:
  • CN 2: Pupils equal and reactive to light 3 =>2 mm OU slightly sluggish. Monocular vision tested. Visual fields intact to finger counting OD. No vision detected (peripheral or central) to finger counting, finger wagging, or to light OS. No intraocular hemorrhage visualized
  • CN 3 - CN 12: grossly normal
Imaging

- MRI contraindicated
- CTA Head:
  1. No acute infarct or hemorrhage.
  2. No high-grade stenosis or occlusion of the intracranial vasculature.
  3. Dilated left superior ophthalmic vein which drains into a dilated angular vein along the nasal ridge and facial vein more inferiorly. Metallic artifact within the region of the left orbital apex likely correlates with prior treatment of the cavernous carotid fistula and obscures evaluation of the adjacent cavernous sinus. Although, a dilated superior ophthalmic vein can be seen after carotid cavernous fistula treatment this finding is expected to decrease over time and comparison with outside studies is needed to assess for this interval change with is not currently available. A persistently dilated superior ophthalmic vein raises concern for persistent carotid cavernous fistula.
Next Steps
Pathogenesis of Hypercoagulability in HbSS

• Intrinsic
  • Increased platelet activation
  • Depletion of normal anticoagulant proteins
  • Increased expression of Tissue Factor
  • HbSC & HbSβ+thal > HbSS & HbSβ0thal
  • Autosplenectomy
  • RBC membrane abnormalities

• Extrinsic
  • Increased hospitalizations
  • Indwelling catheters
  • Orthopedic surgeries / avascular necrosis
  • Pregnancy

RBCX

- ASFA Category I (Grade 1C)
<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.</td>
</tr>
<tr>
<td>II</td>
<td>Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.</td>
</tr>
<tr>
<td>III</td>
<td>Optimum role of apheresis therapy is not established. Decision making should be individualized.</td>
</tr>
<tr>
<td>IV</td>
<td>Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.</td>
</tr>
</tbody>
</table>

ASFA Guidelines
Categories

### ASFA Guidelines

#### Grades

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Description</th>
<th>Methodological quality of supporting evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1A</td>
<td>Strong recommendation, high-quality evidence</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
<td>Strong recommendation, can apply to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>Grade 1B</td>
<td>Strong recommendation, moderate quality evidence</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies</td>
<td>Strong recommendation, can apply to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>Grade 1C</td>
<td>Strong recommendation, low-quality or very low-quality evidence</td>
<td>Observational studies or case series</td>
<td>Strong recommendation but may change when higher quality evidence becomes available</td>
</tr>
<tr>
<td>Grade 2A</td>
<td>Weak recommendation, high-quality evidence</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
<td>Weak recommendation, best action may differ depending on circumstances or patients’ or societal values</td>
</tr>
<tr>
<td>Grade 2B</td>
<td>Weak recommendation, moderate-quality evidence</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies</td>
<td>Weak recommendation, best action may differ depending on circumstances or patients’ or societal values</td>
</tr>
<tr>
<td>Grade 2C</td>
<td>Weak recommendation, low-quality or very low-quality evidence</td>
<td>Observational studies or case series</td>
<td>Very weak recommendations; other alternatives may be equally reasonable</td>
</tr>
</tbody>
</table>

RBCX

- ASFA Category I (Grade 1C)
- Goal:
  - Reduce percentage of HbS to ≤ 30% of total hemoglobin
  - Total hemoglobin approximately but not greater than 10 g/dL
RBCX in HbSS Acute Stroke

**Pros**
- Treats underlying disease etiology
- Strong evidence
- Has role in prevention (Category 1 / Grade 1A)

**Cons**
- Requires high-throughput venous access
- Requires multiple RBC units
- Often requires antigen matching
- Extensive BB workup for new patients
- Delay in treatment
- Not available everywhere

Hulbert ML. *J Pediatr* 2006; 149:710.
Coexistent Sickle Cell Disease Has No Impact on the Safety or Outcome of Lytic Therapy in Acute Ischemic Stroke: Findings From Get With The Guidelines-Stroke

Robert J. Adams, MS, MD; Margueritte Cox, MS, MGIST; Shelly D. Ozark, MD; Julie Kanter, MD; Phillip J. Schulte, PhD; Ying Xian, MD, PhD; Gregg C. Fonarow, MD; Eric E. Smith, MD, MPH; Lee H. Schwamm, MD

*Stroke.* March 2017
tPA

- Useful only in **ischemic** strokes
  - HbSS have more hemorrhagic (26%) when compared with controls (18%; $p \leq 0.001$)
  - Ischemic are overall more common for HbSS and controls
MOA of tPA

*Henry’s. 22nd ed, 2011.*
Adams et al Findings

- HbSS are more likely to:
  - Arrive without ambulance
  - Longer time since symptom onset at presentation
  - Have previous stroke
  - Have prosthetic heart valve
  - Present to teaching hospital

- HbSS are less likely to:
  - Have DMII, HTN
  - Smoke
Table 2. Lytic Therapy and Safety Among SCD and Non-SCD Cohorts, After Matching on Age, Sex, and Black Versus Nonblack Race

<table>
<thead>
<tr>
<th>Variable</th>
<th>SCD (n =832)</th>
<th>Non-SCD (n =3328)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombolytic therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any thrombolytic therapy, n (%)</td>
<td>61 (8.2)</td>
<td>290 (9.4)</td>
<td>0.3024</td>
</tr>
<tr>
<td>Thrombolytic therapy types among patients receiving thrombolytic therapy, n (%)</td>
<td></td>
<td></td>
<td>0.9818</td>
</tr>
<tr>
<td>Intravenous tPA only</td>
<td>46 (82.1)</td>
<td>223 (61.1)</td>
<td></td>
</tr>
<tr>
<td>IA tPA only</td>
<td>8 (14.3)</td>
<td>42 (15.3)</td>
<td></td>
</tr>
<tr>
<td>Both intravenous tPA and IA tPA</td>
<td>2 (3.6)</td>
<td>10 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Onset to treatment time in min, median (25th–75th percentile)</td>
<td>148 (100–179)</td>
<td>145 (115–171)</td>
<td>0.6602</td>
</tr>
<tr>
<td>Door-to-needle time in min, median (25th–75th percentile)</td>
<td>73 (52–99)</td>
<td>79 (58–101)</td>
<td>0.3891</td>
</tr>
<tr>
<td>Arrive by 2 h, treat with intravenous tPA by 3 h</td>
<td>32 (78.1)</td>
<td>189 (79.1)</td>
<td>0.8814</td>
</tr>
<tr>
<td>Complications of thrombolytic therapy*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>3 (4.9)</td>
<td>9 (3.2)</td>
<td>0.4502</td>
</tr>
<tr>
<td>Life-threatening systemic hemorrhage</td>
<td>0 (0.0)</td>
<td>2 (0.7)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Other serious complication</td>
<td>1 (1.6)</td>
<td>7 (2.5)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Any serious complication</td>
<td>4 (6.6)</td>
<td>17 (6.0)</td>
<td>0.7732</td>
</tr>
</tbody>
</table>

IA indicates intra-arterial; ICH, intracerebral hemorrhage; SCD, sickle cell disease; and tPA, tissue-type plasminogen activator.
RBCX vs tPA

- No clear guidance
- Case and institution dependent
- RBCX requires apheresis catheter or port
Clinical Course

- tPA given
- No immediate change in vision
- Patient admitted
- Line could not be placed for $\geq 6$h following tPA
- Patient insisted on GA for line placement
Call from Blood Bank

- O Rh positive
- Partial phenotype:
  - Kell: mixed field
  - E: mixed field
  - C: mixed field
- Antibody screen: negative
33 y.o. female with a reported history of sickle cell disease who presents with sudden onset of vision loss, who subsequently left hospital AMA.

**FINAL DIAGNOSIS**
- Normal HPLC
- Normochromic anemia

<table>
<thead>
<tr>
<th>HPLC INTERPRETATION</th>
<th>Hemoglobin</th>
<th>Results</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hgb A₂</td>
<td>2.4%</td>
<td>2.0 - 2.9%</td>
</tr>
<tr>
<td></td>
<td>Hgb F</td>
<td>0%</td>
<td>0 - 1.1%</td>
</tr>
<tr>
<td></td>
<td>Hgb A</td>
<td>97.6%</td>
<td>(96 - 97.9%)</td>
</tr>
<tr>
<td></td>
<td>Hgb S</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

**MICROSCOPIC DESCRIPTION**
- RBCs show a degree of anisocytosis, with hypochromic and normochromic forms. No sickle cells are noted.
- WBCs appear normal.
- Platelets appear normal and are present in normal numbers.
### Component Name | Value | Ref Range
--- | --- | ---
RBC Count | 3.0 (L) | 3.80 - 5.10 M/uL
Hemoglobin | 9.0 (L) | 11.7 - 15.5 g/dL
Hematocrit | 26.5 (L) | 35.0 - 45.0 %
MCV | 88.1 | 80.0 - 100.0 fL
MCH | 30.0 | 27.0 - 33.0 pg
RDW | 18.9 (H) | 11.0 - 15.0 %
Hemoglobin A1 | 97.6 | GREATER THAN 96.0 %
Fetal Hemoglobin | 0.0 | LESS THAN 2.0 %
Hemoglobin A2, Quant | 2.4 | 1.8 - 3.5 %

**Interpretation**

SEE NOTE

Comment:

Note

Normal phenotype.
Summation

- No history of HbSS found
- Multiple interventions for presumed HbSS
- Multiple CareEverywhere notes regarding drug-seeking and malingering
- Patient left AMA
Remaining questions

- Should HbSS patients with no history receive benchtop HbSS screening?
  - Peripheral smear
  - Metabisulfite test / SICKLEDEX
Remaining questions

• Should adjusted weight vs actual weight be used when calculating RBCX volume?

• Weight: 135 kg
  • Actual: 135 kg * 65 mL/kg = 8,775 mL
  • Adjusted: 135 * 50 mL/kg = 6,750 mL
  • Terumo App: 6,218 mL

• With FCR of 30% and Hct of 29%, need:
  • Terumo App: 3,585 mL (~12 units)
Questions

Thanks to Dr. Suchi Pandey & Dr. David Unold