ASFA 2015 Consensus Conference: RBC Exchange in Sickle Cell Disease

Session 5B: SELECTION OF RED CELLS

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Disclosures

- No Conflicts of Interest to disclose.
Given that practice variability exists regarding the extent (full versus partial) of phenotype matching during RBCx procedures...
Questions for Discussion

1. What evidence/guidelines exist for using phenotype matched units during RBCx to prevent alloimmunization?

2. If partial phenotypes are used, which antigens should be matched?

3. What is the cost-benefit ratio of phenotype matching?
Risks of Transfusion

- Allo and Auto-antibody formation
- Hemolytic transfusion reactions
- Overload (iron, volume)
- Hyperviscosity
- SCD crisis
- Infectious diseases
Evidence for Phenotype Matching

- 1990 Vichinsky et al, NEJM
  - Alloimmunization in Sickle Cell Anemia and Transfusion of Racially Unmatched Blood
- 1990 Rosse, Blood
  - Transfusion and Alloimmunization in Sickle Cell Disease
- 2001 Vichinsky et al, Transfusion
  - Prospective RBC Phenotype Matching in a Stroke Prevention Trial for Sickle Cell Anemia: A Multi-center Transfusion Trial
Red Cell Immunization

- **Alloimmunization**
  - 5-12% vs. 25-30% average in SCD
  - Difficulty obtaining compatible blood
    - SCD patients single largest user of rare donor blood (20-30%)

- **Auto-antibody formation**
  - Associated with previous sensitization
  - 8% in SCD
Hemolytic Transfusion Reactions

- **Acute**
- **Delayed**
  - Occurs 5 to 20 days after transfusion
  - Due to antibodies undetectable when compatibility testing performed
- **Sickle Cell Hemolytic Transfusion Reaction**
  - “hyperhemolysis”: patient destroys transfused & own RBCs; bone marrow suppression causing severe anemia ⇒⇒ potentially fatal
Guidelines Supporting Use of Phenotypically Matched Blood


- NIH Management of SCD Monograph (Red Book)
  1) Pre-storage leukocyte reduced RBCs
  2) RBC phenotyping of patient red cells
  3) Permanent record of phenotype in blood bank; copy given to pt./family
  4) Matching for C, E, K usually performed unless pt. has antibodies
  5) RBCs should be screened for sickle trait
NHLBI Evidence Based Guidelines for Management of Sickle Cell Disease


- RBC units that are to be transfused to individuals with SCD should include matching for C, E, and K antigens. *(Moderate Recommendation, Low-Quality Evidence)*

- Executive Summary: JAMA 2014

- GAPS: Recommendations for Research: AJH 2015
Four RCTs, 63 longitudinal and cross-sectional studies, and 46 case reports were identified that demonstrated alloimmunization. In the four RCTs (with >1,100 patients), alloimmunization/autoimmunization development rates ranged between 3 percent and 29 percent.

In the other 63 studies (involving >6,000 patients), alloimmunization rates ranged between 6 percent and 85 percent, and autoimmunization rates ranged between percent and 10 percent.

Overall, minimal evidence is available to support a particular method to reduce or prevent side effects from RBC transfusion.⁴⁰⁷
The systematic review did not identify comparative effectiveness studies that explored different cross-matching approaches. Two studies (one RCT and one observational study involving 159 patients) that implemented stricter matching criteria had more favorable results (alloimmunization rates <7 percent). The definition of a “strict cross match” varied among studies, and often included matching for ABO and a number of other RBC antigens, including DCcEe and Kell, and occasionally Kidd and Duffy.

In the published studies, to prevent alloimmunization or to transfuse patients who were already alloimmunized, investigators most commonly opted to use strictly phenotype-matched RBC units.
Questions for Discussion

1. What evidence / guidelines exist for using phenotype matched units during RBCx to prevent alloimmunization?

2. *If partial phenotypes are used, which antigens should be matched?*

3. What is the cost-benefit ratio of phenotype matching?
Specificity of Alloantibodies Observed in Patients with SCD

<table>
<thead>
<tr>
<th>Antibody</th>
<th>N</th>
<th>% of Patients Sensitized</th>
<th>% of Patients 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-Fy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>62</td>
<td>18.3</td>
<td>3.4</td>
</tr>
</tbody>
</table>

### Incidence of Nonpersistent Alloantibodies

<table>
<thead>
<tr>
<th>Specificity</th>
<th>Incidence In Study</th>
<th>Incidence Analyzed</th>
<th>Nonpersistent* No.</th>
<th>Nonpersistent* %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-D</td>
<td>44</td>
<td>19</td>
<td>5</td>
<td>26.3</td>
</tr>
<tr>
<td>Anti-C</td>
<td>102</td>
<td>27</td>
<td>11</td>
<td>40.7</td>
</tr>
<tr>
<td>Anti-E</td>
<td>143</td>
<td>50</td>
<td>16</td>
<td>32.0</td>
</tr>
<tr>
<td>Anti-V</td>
<td>8</td>
<td>4</td>
<td>1</td>
<td>25.0</td>
</tr>
<tr>
<td>Anti-c</td>
<td>10</td>
<td>3</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Anti-M</td>
<td>26</td>
<td>8</td>
<td>3</td>
<td>37.5</td>
</tr>
<tr>
<td>Anti-S</td>
<td>31</td>
<td>5</td>
<td>2</td>
<td>40.0</td>
</tr>
<tr>
<td>Anti-K</td>
<td>95</td>
<td>36</td>
<td>11</td>
<td>30.6</td>
</tr>
<tr>
<td>Anti-Fy\textsuperscript{a}</td>
<td>62</td>
<td>17</td>
<td>8</td>
<td>47.1</td>
</tr>
<tr>
<td>Anti-Jk\textsuperscript{b}</td>
<td>36</td>
<td>7</td>
<td>3</td>
<td>42.9</td>
</tr>
</tbody>
</table>

*A nonpersistent antibody is one that was not detectable on two occasions at a time greater than 1 year after initial detection.
## Selected Antigen Frequencies By Race/Ethnicity

<table>
<thead>
<tr>
<th>Blood Group</th>
<th>Antigen Frequency</th>
<th>Caucasians</th>
<th>African Americans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td></td>
<td>85</td>
<td>92</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>E</td>
<td></td>
<td>30</td>
<td>19</td>
</tr>
<tr>
<td>Kell</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K</td>
<td></td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Kidd</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jk&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>77</td>
<td>92</td>
</tr>
<tr>
<td>Jk&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>74</td>
<td>49</td>
</tr>
<tr>
<td>MNS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td></td>
<td>55</td>
<td>31</td>
</tr>
<tr>
<td>s</td>
<td></td>
<td>89</td>
<td>97</td>
</tr>
<tr>
<td>Duffy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fy&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>66</td>
<td>10</td>
</tr>
<tr>
<td>Fy&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>83</td>
<td>23</td>
</tr>
</tbody>
</table>
Literature: Probability of finding compatible blood

- 1/33 vs. 1/4
  - Difference of a compatible unit lacking the 3 most common antigens (C, E, K,) missing on RBCs of African Americans in a typical donor pool (90% Caucasian & <10% African American) vs. African American only donor pool
  - 24X more likely to find a compatible unit
    - lacking 9 of the most common antigens causing alloimmunization in SCD patients if blood is selected from an African American donor

Sosler

Castro et al.
# Probability of finding compatible blood: Rare Traits

<table>
<thead>
<tr>
<th>Rare Trait</th>
<th>Caucasians</th>
<th>African Americans</th>
</tr>
</thead>
<tbody>
<tr>
<td>U Negative</td>
<td>None Found</td>
<td>1 in 250</td>
</tr>
<tr>
<td>Js(b) Negative</td>
<td>None Found</td>
<td>1 in 319</td>
</tr>
<tr>
<td>Cr(a) Negative</td>
<td>None Found</td>
<td>1 in 6,429</td>
</tr>
<tr>
<td>At(a) Negative</td>
<td>None Found</td>
<td>1 in 16,400</td>
</tr>
</tbody>
</table>

Source: ARC, Mid-Atlantic Region 2002
African American Blood Donors

- 5% of eligible Americans donate blood
  - of those ≈ 10% are African American

- Increased minority donors
  - % African Americans nationally has not change significantly (REDS I, REDS II)
  - African American Recruitment Campaigns
    “Our blood makes a difference!”
Impact of Differences in Donation Rates

- Increased risk of transfusion associated morbidity
- Difficulty in finding compatible blood
- Delay in care/use of non-optimal blood
- Use of national rare blood inventory
  - SCD patients single largest users (20-30%)
Questions for Discussion

1. What evidence / guidelines exist for using phenotype matched units during RBCx to prevent alloimmunization?

2. If partial phenotypes are used, which antigens should be matched?

3. What is the cost-benefit ratio of phenotype matching?
RBC transfusion

- Determine the efficacy of chronic transfusions to prevent or treat a number of complications of SCD, including treatment of chronic pain syndromes, treatment of recurrent priapism, treatment of pulmonary hypertension, prevention of stroke in adults, and prevention of chronic kidney disease.
- Determine the efficacy and cost-effectiveness of routinely providing phenotypically matched RBCs to all patients with SCD undergoing RBC transfusion.
- Clarify the need for perioperative transfusions in patients with different genotypes undergoing surgical procedures of varying risk.
- Determine the optimal target HbS concentration for patients with SCD who receive chronic transfusion therapy.
- Compare the cost-effectiveness and morbidities of simple versus exchange techniques for chronic transfusion.
- Determine the optimal time to initiate chelation therapy and to establish the best diagnostic tool for determining iron overload in patients with SCD.
- Assess the effects of transfusion-related hyperviscosity, which will require methods for accurate measurement. In addition, studies are needed to determine the best ways to avoid hyperviscosity from transfusion.
Additional Factors: Alloimmunization

- RBCs Storage & Alloimmunization
  - Zalpuri et al, Transfusion 2013
- “Responders” determination
- Impact of Inflammation
- Blood Group Antigens as Biologic Mediators
- Practice Variability
- Defining Outcomes (reduction, elimination, etc.)
Blood Banks’ Use of Phenotypically Matched Blood

- Osby et al. 2004 (Archives of Pathology & Lab Med)
- Afenyi-Annan and Brecher 2004 (Transfusion, Letter to Editor)
- Afenyi-Annan, 2004 (Oral presentation, RWJ-Clinical Scholars, Published Abstract/Invited Oral presentation, AABB 2005, etc)
- Afenyi-Annan, Konrad, and Lottenberg 2005 (Transfusion)
Extended Phenotype Matching Cost Effective?: Recent Literature

Alloimmunization During RBCs Selected for Patients w/SCD

- Telen MJ, Afenyi-Annan A, Garrett ME et al. (Transfusion 2014; epub December 03)
Extended Phenotype Matching (example)

- Sample University Hospital Costs
  - CEK (performed in house) = approx. $430/unit
  - CEK (performed by outside Supplier) = approx. $460/unit
- Reagents (increased tremendously), MT skill/time
- If order additional antigen’s negative approx. = $93/antigen
- Frozen Blood/Rare = additional $450+
  - Not including cost of Onsite deglycerize
Considerations for Extended Phenotype Matching: Determining Cost/Benefit

- MUST CLEARLY DEFINE
  - Direct Costs:
  - Indirect Costs:
  - Patient Costs:
  - Societal Costs:

*** MORAL AND ETHICAL DUTY DESPITE COSTS
**Future of Extended Phenotype Matching**

<table>
<thead>
<tr>
<th>COST</th>
<th>BENEFIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selecting for minority of patients</td>
<td></td>
</tr>
<tr>
<td>Serology to genotyping both donors and recipients</td>
<td>Better matching at Rh loci</td>
</tr>
<tr>
<td>Decreased alloimmunization?</td>
<td>Decreased alloimmunization</td>
</tr>
<tr>
<td>Prospective testing for minority of patients</td>
<td></td>
</tr>
<tr>
<td>Infrequent transfusion &gt; alloimmunization</td>
<td></td>
</tr>
</tbody>
</table>
Discussion: Topic 2

- Are there any advantages of using fresh blood (<7 days old), either for acute or chronic RBCx?
### “Red Cell Storage Lesion”

<table>
<thead>
<tr>
<th>INCREASE</th>
<th>DECREASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate (LDH), Pyruvate, Ammonia</td>
<td>ATP</td>
</tr>
<tr>
<td>Intracellular Na</td>
<td>2,3-DPG (depleted by 14 days)**</td>
</tr>
<tr>
<td>Membrane vesicles, lipids</td>
<td>pH</td>
</tr>
<tr>
<td>Superoxides, Free Radicals</td>
<td>Intracellular K</td>
</tr>
<tr>
<td>Plasma Hemoglobin</td>
<td></td>
</tr>
<tr>
<td>Plasma K</td>
<td></td>
</tr>
<tr>
<td>% Hemolysis</td>
<td></td>
</tr>
<tr>
<td>% Viable Cells (24hrs Post-Transfusion)</td>
<td></td>
</tr>
</tbody>
</table>
Figure 8-1. Oxygen dissociation curves under different conditions.
Thank You!
Questions?
Is there any advantage of one preservative system over another (e.g., CPDA1 vs AS1 vs AS3)?
# Whole Blood and RBCs in Different Additive Solutions

<table>
<thead>
<tr>
<th>Variable</th>
<th>CPD</th>
<th>CPDA-1</th>
<th>AS-1&lt;sup&gt;+&lt;/sup&gt;</th>
<th>AS-3&lt;sup&gt;†&lt;/sup&gt;</th>
<th>AS-5&lt;sup&gt;†&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days of Storage</td>
<td>0</td>
<td>21</td>
<td>0</td>
<td>35</td>
<td>42</td>
</tr>
<tr>
<td>% Viable cells (24 hours posttransfusion)</td>
<td>100</td>
<td>80</td>
<td>100</td>
<td>79</td>
<td>71</td>
</tr>
<tr>
<td>pH (measured at 37°C)</td>
<td>7.20</td>
<td>6.84</td>
<td>7.60</td>
<td>6.98</td>
<td>6.71</td>
</tr>
<tr>
<td>ATP (% of initial value)</td>
<td>100</td>
<td>86</td>
<td>100</td>
<td>56 (±16)</td>
<td>45 (±12)</td>
</tr>
<tr>
<td>2,3-DPG (% of initial value)</td>
<td>100</td>
<td>44</td>
<td>100</td>
<td>&lt;10</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Plasma K+ (mmol/L)</td>
<td>3.9</td>
<td>21</td>
<td>4.20</td>
<td>27.30</td>
<td>78.50&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>Plasma hemoglobin (mg/L)</td>
<td>17</td>
<td>191</td>
<td>82</td>
<td>461</td>
<td>658.0&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>% Hemolysis</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

* Based on information supplied by the manufacturer.
† From Simon, et al.
‡ Values for plasma hemoglobin and potassium concentrations may appear somewhat high in 35-day stored RBC units; the total plasma in these units is only about 70 mL.
Additional Questions: 2

Are there any unintended consequences associated with selecting phenotyped red cells; and if so, should they be prospectively prevented?
Possible Unintended Consequences

- Selection Bias for African, African American Population
  - Other hemoglobinopathies: HbC, HbE (detect
  - Increased hemolysis, i.e. G6PD red cells (<1% vs 12-13%)
- Shifting antibody frequencies (Anti-V, anti-S, anti-MNS Anti Js\(^a\))
- ?? Change in alloimmunization rates
  - genotypic variation in RH DCE among BOTH African American donors & recipients
Should Be Prospectively Avoided?

- Likely Not cost effective
- Low prevalence
- Increased cost/unit
- Identifiable post-transfusion, if considered