Red blood cell alloimmunization and delayed hemolytic transfusion reactions in patients with sickle cell disease

Jeanne Hendrickson, MD
December 17, 2018
RBC Alloimmunization

- Occurs after exposure to non-self blood group antigens, through RBC transfusion, IV drug use, or pregnancy

Adapted from E. Sjöberg Webster, reproduced by Tormey et al, Blood 2018 in preparation
RBC Alloimmunization

- Increases the risk of immediate as well as delayed hemolytic transfusion reactions
- May lead to lengthy and costly blood product delays
- Increases the risk of hemolytic disease of the newborn
RBC Alloimmunization

- Occurs in approximately 3-5% of “general” transfused adults

REDS-III Recipient Database, with 6,597 alloimmunized patients

Karafin et al, BJH 2018
Antibodies associated with fatalities: anti-Jk\(^a\), -Jk\(^b\), -K, -E, -c, -C, -Fy\(^a\), -Fy\(^b\), -S, -Co\(^b\), -M, and others (including 2 reactions with hyperhemolysis)
Dangers of Delayed Hemolytic Transfusion Reactions (DHTRs)

- Bystander hemolysis or hyperhemolysis, an under-reported transfusion complication, is a cause of morbidity and mortality in patients with sickle cell disease
- Poorly understood
- US-wide research registry is in the process of being developed
RBC Alloantibodies and Morbidity

- Data from the UK Serious Hazards of Transfusion (SHOT) report provide insight into both morbidity and mortality associated with non-ABO alloantibodies
- For DHTRs occurring between 2006-14:
  - ~60% associated with mild-moderate morbidity
  - ~10% associated with severe morbidity

The United Kingdom’s independent, professionally-led haemovigilance scheme.

http://www.shotuk.org/home/
More Than 70% of RBC Antibodies Fall Below the Level of Blood Bank Detection at Some Point ("Evanescence")

Thus, the prevalence of RBC alloimmunization is significantly underestimated.
## Evanescence Rates by Antibody Specificity

<table>
<thead>
<tr>
<th>Evanescence Rate In General Patients (highest to lowest)</th>
<th>Evanescence Rate In SCD (highest to lowest) (^{22,23})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu(^a) (65%; 11/17)*</td>
<td>Js(^a) (80%; 12/15)*</td>
</tr>
<tr>
<td>C(^w) (61%; 19/31)*</td>
<td>Fy(^b) (78%, 7/9)</td>
</tr>
<tr>
<td>Jk(^b) (54%; 7/13)</td>
<td>S (66%, 14/22)</td>
</tr>
<tr>
<td>Le(^b) (52%; 13/25)</td>
<td>Jk(^b) (58%; 11/19)</td>
</tr>
<tr>
<td>P(_1) (50%; 9/18)</td>
<td>Le(^a) (54%; 14/26)</td>
</tr>
<tr>
<td>Jk(^a) (49%; 30/61)</td>
<td>Fy(^a) (51%; 18/35)</td>
</tr>
<tr>
<td>Le(^a) (47.5%; 19/40)</td>
<td>C (47%; 27/57)</td>
</tr>
<tr>
<td>E (38%; 134/353)</td>
<td>Go(^a) (43%; 3/7)*</td>
</tr>
<tr>
<td>K (32%; 117/366)</td>
<td>E (41%; 37/90)</td>
</tr>
<tr>
<td>M (30%; 12/40)</td>
<td>K (41%; 23/56)</td>
</tr>
<tr>
<td>S (30%; 8/27)</td>
<td>Le(^b) (40%; 4/10)</td>
</tr>
<tr>
<td>c (27%; 23/84)</td>
<td>V (39%; 7/18)*</td>
</tr>
<tr>
<td>C (19%; 21/109)</td>
<td>M (38%; 3/8)</td>
</tr>
<tr>
<td>Fy(^a) (17%; 16/94)</td>
<td>D (36%; 10/28)</td>
</tr>
<tr>
<td>D (12%; 32/262)</td>
<td>c (0%; 0/5)</td>
</tr>
</tbody>
</table>
RBC Alloantibodies: Challenges in Detection

■ What is a major reason for not detecting blood group alloantibodies?
  ■ Evanescence

■ If we do detect antibodies, why aren’t we preventing the complications of alloimmunization?
  ■ Patients may seek treatment at different hospitals

■ What are our actual opportunities to detect non-ABO blood group antibodies?
  ■ Missed alloimmunization
How Many Antibodies Are We Detecting with Random Testing?

Based on established kinetics of antibody induction and evanescence and with some fancy mathematics based on follow-up testing data...

It is estimated that only about 30-32% of transfusion-induced antibodies are likely detected by routine, non-systematic type and screen testing.

Stack G, Tormey CA. Transfusion 2016
Responders/Non-Responders

Higgins and Sloan, Blood 2008
Factors Potentially Contributing to Alloantibody Responses:

**Potential RBC Unit Factors**
- Storage age / storage duration of a unit
- Component modifications (e.g., leukoreduction, irradiation)
- Storage lesion / incurred damage
- Microparticles or cellular contaminants (e.g., platelets)

**Potential Donor Factors**
- Degree of antigen mismatch between donor/recipient
- Susceptibility of donor RBCs to destruction or lysis (e.g., osmotic fragility)
- Donor demographics (e.g., age, gender, ethnicity)
- Underlying donor disorder (e.g., G6PD deficiency)

**Potential Antigen Factors**
- Immunogenicity of a given antigen
- Variants / genetic heterogeneity within antigen systems
- Density / copy number of a given antigen

**Potential Recipient Factors**
- Degree of antigen mismatch between recipient/donor
- HLA type / antigen recognition ability
- Immune status (e.g., marrow suppression, immunosuppressive drugs, co-existing autoantibodies, +DAT)
- Recipient demographics (e.g., age, gender, ethnicity)
- Underlying recipient general disease (e.g., thalassemia, myelodysplastic syndrome)
- Disease-associated inflammation (e.g., chronic autoimmune disease, viral infection, acute chest syndrome in sickle cell disease)
- RBC transfusion burden / prior antigen exposures

Tormey et al, Blood 2018 in preparation
REDS-III Recipient Database: Female Patients Were More Likely than Males to be Alloimmunized At Any Point During the 4 Year Study Duration
# Disease Status Impacts RBC Alloimmunization

<table>
<thead>
<tr>
<th>Population or disease state</th>
<th>Reported alloimmunization rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General adult patients</strong></td>
<td></td>
</tr>
<tr>
<td>Retrospective analysis</td>
<td>1-3</td>
</tr>
<tr>
<td>Prospective analysis</td>
<td>8-10</td>
</tr>
<tr>
<td><strong>Hemoglobin disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>19-43</td>
</tr>
<tr>
<td>Thalassemia major</td>
<td>5-45</td>
</tr>
<tr>
<td><strong>Inflammatory disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Autoimmune disorders, general</td>
<td>16</td>
</tr>
<tr>
<td>Inflammatory bowel diseases</td>
<td>8-9</td>
</tr>
<tr>
<td><strong>Lymphoid disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Acute lymphoid leukemia</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>2-3</td>
</tr>
<tr>
<td><strong>Myeloid disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>3-16</td>
</tr>
<tr>
<td>Myelodysplastic syndromes (includes myelodysplastic/myeloproliferative disorders)</td>
<td>15-59</td>
</tr>
<tr>
<td>Solid tumors, nonhematopoietic</td>
<td>1-10</td>
</tr>
<tr>
<td><strong>Transplantation</strong></td>
<td></td>
</tr>
<tr>
<td>Hematopoietic progenitor cell</td>
<td>1-4</td>
</tr>
<tr>
<td>Liver transplant</td>
<td>4-23</td>
</tr>
<tr>
<td>Other sites or multiple organ transplantation</td>
<td>1-10</td>
</tr>
</tbody>
</table>

![RBC Alloantibody Prevalence](chart.png)
REDS-III Recipient Database: The odds ratio of being a “responder” as compared to a “non-responder” in the presence of a particular diagnosis
The Unanswered Question: Why Do So Many Patients with SCD Form Alloantibodies?

- More RBC exposure than the average transfused individual
  - RBC exposure during times of illness/inflammation may be unavoidable
- Baseline inflammation with free heme and leukocytosis and thrombocytosis, among others
- RH genetic diversity
Matzinger’s “Danger” Theory

Matzinger, Science 2002
Human Data: Inflammation and RBC Alloimmunization

Does a febrile reaction to platelets predispose recipients to red blood cell alloimmunization?
Yazer et al, Transfusion 2009

High Risk of Transfusion-induced Alloimmunization of Patients with Inflammatory Bowel Disease
Papay et al, Am J Medicine 2012

Red Blood Cell Alloimmunization Is Influenced By Recipient Inflammatory State At Time Of Transfusion In Patients With Sickle Cell Disease
Fasano et al, BJH 2015
Chronic inflammatory autoimmune disorders are a risk factor for red blood cell alloimmunization

Ryder et al, BJH 2015

Red cell alloimmunisation in patients with different types of infections

Evers et al, BJH 2016
Disseminated Viral Infection: Non-significant ↑ relative risk of RBC alloimmunization
- RR = 2.41

Poly(I:C) ~ viral dsRNA:
- ↑ alloimmunization

Viral Inflammation Increases Alloimmunization

Evers et al, Br J Haematol 2016

Anti-RBC IgG

Smith et al, Blood 2012
All Inflammation is Not the Same: Gram Negative Bacteremia Decreases Alloimmunization

- **Gram-negative bacteremia**: ↓ Risk of alloimmunization
  - RR = 0.58

- **LPS treatment**: ↓ alloimmunization

---

**Red cell alloimmunisation in patients with different types of infections**

Evers et al, Br J Haematol 2016

---

**Anti-RBC IgG**

Poly(I:C) = dsRNA, mimics RNA viral infections
- Induces **Type 1 Interferons** (IFNα/β)


IFNα/β Receptor Signaling is Required for RBC Alloimmunization in an Animal Model

Gibb et al, JI 2017
Blockade of the MAVS or IRF 3/7 Pathways Mitigate the Effect of Poly (I:C) on Alloimmunization

Gibb et al, JI 2017
Recipient Flu Infection Increases Alloimmunization in a Type 1 IFN Dependent Manner

Could Patients with SCD Have High Type 1 Interferon Levels?

Random blood sampling, preliminary data
The RBC Autoantibody/RBC Alloantibody Association

- In MDS patients, 65% with alloantibodies also had autoantibodies (Singhal et al, Haematologica 2017)
- In children with SCD, 69% with alloantibodies also had autoantibodies (Nickel et al, AJH 2015)
- In thalassemia patients, 50% with alloantibodies also had autoantibodies (Dhawan et al, ASTS 2014)

Is there a type 1 IFN connection?
The RBC Autoantibody/RBC Alloantibody Association

- Some previously identified autoantibodies are likely alloantibodies associated with Rh variant antigens
- Autoantibodies are also found, however, in diseases associated with allommunization
Could some “antibody negative” DHTRs be due to antibodies (such as those in the Dombrock family) that are difficult to detect using traditional blood bank methodology?

Could some “antibody negative” DHTRs be due to alloantibodies characterized as autoantibodies?
RBC Alloimmunization in Patients with SCD is a Bigger Problem.
RBC Alloimmunization in Patients with SCD is a Bigger Problem . . . Than Meets the Eye
Thank You