Challenges of Transfusion in Sickle Cell Disease: A Case Study

Nabiha Huq Saifee MD, PhD

June 2017
Case: 29 year old woman

Day -7
B positive
Negative antibody screen

Day -5
2 RBCs transfused for HCT 18%

Day 0
Admission to community hospital
Order for 2 more RBCs for HCT 17%

Day 1
B positive
Positive antibody screen
Case: 29 year old woman

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Day 1
B positive
Positive antibody screen

Are you worried about the newly positive antibody screen?
Case: 29 year old woman

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B positive
Negative antibody screen

Day -5
2 RBCs transfused for HCT 18%

Day 0
Admission to community hospital
Order for 2 more RBCs for HCT 17%

Day 1
B positive
Positive antibody screen

Are you worried about the newly positive antibody screen?

Anti-C, anti-S, anti-M
Newly positive antibody screen less than 7 days from transfusion

- **Delayed hemolytic transfusion reaction (DHTR)**
  - Destruction of transfused RBCs due to amnestic response of previously formed antibodies

- **Delayed serologic transfusion reaction (DSTR)**
  - Evidence of RBC sensitization but not destruction of transfused RBCs
Immunohematology Work-up of Transfusion Reaction

- Clerical check
- Repeat ABO typing on pre- and post-transfusion samples
- Hemolysis check
- DAT
The concepts on this slide (ie, transfusion reaction investigation) takes 5 slides. Do you have a way to reduce it to 2-3 slides?

Options:
Do not show the next slide and just mention the results
Add animation to populate the result

Pagano, Monica B, 6/22/2017
Immunohematology Work-up of Transfusion Reaction

✓ Clerical check: no errors noted

✓ Repeat ABO typing on pre- and post- transfusion samples: match

✓ Hemolysis check: **Positive**

⚠ DAT:
Immunohematology Work-up of Transfusion Reaction

✓ Clerical check: no errors noted

✓ Repeat ABO typing on pre- and post- transfusion samples: match

✓ Hemolysis check: **Positive**

✓ DAT: **Positive**
✓ IgG: weak
✓ C3: weak

(Present in both pre- and post-transfusion samples)
Immunohematology Work-up of Transfusion Reaction

- Clerical check: no errors noted
- Repeat ABO typing on pre- and post-transfusion samples: match
- Hemolysis check: Positive
- DAT: Positive
  - IgG: weak
  - C3: weak
- Eluate: anti-C, anti-M
- Antibody identification: anti-C, -S, -M
DHTR versus DSTR

• **Delayed hemolytic transfusion reaction** (DHTR)
  – Destruction of transfused RBCs due to amnestic response of previously formed antibodies

• **Delayed serologic transfusion reaction** (DSTR)
  – Evidence of RBC sensitization but not destruction of transfused RBCs
Case: 29 year old female

- 14 weeks gestational age (G2P0A1)
- Sickle cell HbSS disease
- Admitted with left flank pain for 6-7 days
  - Other symptoms include poor appetite, malaise, subjective fevers, and gross hematuria

Vital signs
- Temperature 37.4
- BP 106/55 mmHg
- P 95 bpm
- RR 22
- O2 sat 99%
- Weight 45.8kg
- Height 5’5”

Labs
- WBC 31.1 k/mcL
- HCT 17%
- Hgb 5.9 g/dL
- Tbil 3.6 mg/dL
- Dbil 0.9mg/dL
- Creatinine 0.36

Urinalysis
- Color Red
- Appearance Clear
- Bilirubin Neg
- Blood Mod
- Protein (mg/dL) 100
- Nitrite Neg
- Leuko-esterase Neg
- WBC 6-10
- RBC 0-2
- Bacteria 1+
Consider options to soften this slide: adding animation, change to smaller font vital signs/labs
Pagano, Monica B, 6/22/2017
Differential

- Sepsis: pyelonephritis
- Sickle pain crisis
- Delayed hemolytic transfusion reaction
- Fetal demise?
Differential

- Sepsis: pyelonephritis
- Sickle pain crisis
- Delayed hemolytic transfusion reaction
- Fetal demise?

Hospitalist wants to transfuse RBCs for goal HCT of 20%. Are you concerned?
# RBC Antigen Expression in Patient and RBC units provided

- >300 antigens on RBC
- All patients matched for ABO and RhD
- RBC antigen matching in sickle cell disease:
  - Standard of care: Rh antigens (C, E) and Kell antigen (K)
  - Few centers: extended phenotype matching
  - Rare: RBC genotype-based matching

## Sample Antigen Expression

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RBC Antigen Expression in Patient and RBC units provided

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Units sent to hospital are crossmatch-compatible and antigen-negative for all known antibodies.
**RBC Antigen Expression in Patient and RBC units provided**

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- For sickle cell disease, our policy is to match for Rh and K.
- Only other common clinically significant antibody patient can make is Fya.
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- For sickle cell disease, our policy is to match for Rh and K.
- Only other common clinically significant antibody patient can make is Fya.
- Note: unit provided is O-negative while patient is B-positive
Rh allele frequencies in Caucasians versus African Americans

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<tr>
<th>Allele</th>
<th>Caucasian</th>
<th>African-American</th>
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<tr>
<td>R1 (D+, C+, E-)</td>
<td>0.42</td>
<td>0.17</td>
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<tr>
<td>Ro (D+, C-, E-)</td>
<td>0.04</td>
<td>0.42</td>
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<tr>
<td>r (D-, C-, E-)</td>
<td>0.37</td>
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Matching for C- and E- phenotype common in individuals of African-American descent contributes to stress on O negative supply.
RBC Antigen Expression in Patient and RBC units provided

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Does this unit meet standard of care for transfusion in sickle cell disease?
Case 1: Transfusion Reaction 2

- 100mL into transfusion of RBC temperature increases from 37.7 to 39 degrees Celsius

- Patient reports headache and increased work of breathing

- Physician evaluates patient and notes lungs are clear, vital signs stable

- Sends for Hgb recheck

- Pre- and post-hemolysis check: Positive

- Pre- and post-DAT: Positive
  - Anti-IgG Weak
  - Anti-C3 Weak
Case 1: Rapid drop in hemoglobin

- Repeat Hgb 3.4/HCT 9% post-transfusion
- LDH 5752 IU/mL
- Reticulocyte index 4.7%

Physician asking what to do?
Recommendations:

• Repeat HCT - make sure the value is real

• Tell physician this is concerning for hyperhemolysis syndrome

• Ask hematology to evaluate and dose IVIG and steroids

• Start RBC transfusion after dosing steroids at least

• Blood bank to provide antigen-matched crossmatch compatible unit (including M and Fya)

• OB evaluation of fetus

• Transfer to ICU for close monitoring
Indications for Transfusion in Sickle Cell Disease

**Episodic**
- Acute symptomatic anemia
- Acute Chest Syndrome
- Aplastic crisis
- Acute Stroke
- Acute splenic or hepatic sequestration
- Acute Multiorgan Failure Syndrome
- Surgery requiring general anesthesia
- Eye Surgery

**Chronic**
- Prevention of first stroke or recurrent stroke
- Complicated pregnancy
- Chronic renal failure

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With Transfusion Comes Risk of Alloimmunization
Red Cell Alloimmunization in Sickle Cell Disease

• About 25% of transfused SCD patients in US will form red cell alloantibodies

• Higher incidence of Delayed Hemolytic Transfusion Reaction and Hyperhemolytic Transfusion Reaction in SCD
  – King’s College Hospital, London over 5 year period
    • evidence of DHTR 7.7% SCD patients or 23/2158 (1.1%) transfusion episodes – 5 severe DHTRs and 2 deaths
  – Henri Mondor Hospital, France during 12 years
    • 99 cases in 69 adult sickle cell patients – 6 deaths

Key Clinical Features of DHTR/Hyperhemolysis Syndrome

• Fever and pain
  – Mimics sickle cell crisis

• Evidence of hemolysis
  – Hemoglobinuria
  – Hyperbilirubinemia
  – Elevated LDH

• Severe anemia
  – post-transfusion HCT/Hb measurement below pre-transfusion level

• Decreased absolute reticulocyte count

• Exacerbation with transfusion

• Early Recognition is Key
  – Difficult due to background chronic hemolysis and sickle cell pain crisis

• Quickly evolves within a few hours:
  – Multiorgan failure
  – Death

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Outcomes in 99 DHTR cases in adult SCD

- 6 deaths and 5 amongst patients receiving additional transfusion

Potential Mechanisms

• Poorly understood
  – DAT positive and DAT negative described
  – Triggers: alloimmunization, hemoglobinopathy (sickle cell, thalassemia)

• Bystander hemolysis
  – Destruction of autologous RBCs

• Suppression of erythropoiesis
  – Reticulocytopenia

• Activated macrophages
  – Aid in destruction of RBCs

Treatment of Hyperhemolysis Syndrome

- **Avoid transfusion**
- Supportive Care
- Promote erythropoiesis
  - Erythropoietin
  - IV iron
- **Immunosuppression:**
  - Steroids
  - IVIG
  - Rituximab
- Eculizumab
- Apheresis
  - Whole blood exchange (1999)
  - Plasma to red cell exchange (2014)

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Registry for Hyperhemolysis Syndrome in Sickle Cell Disease

• Announced at 2016 AABB annual meeting

• Sally Campbell Lee, MD at University of Illinois at Chicago
Case: Treatment and Follow-up

**Treatment**
- Prednisone 1 mg/kg
- IVIG 400 mg/kg/day for 5 days total
- 1 additional RBC transfusion
- Recommend transfuse only if Hct<14 or patient symptomatic

**Follow-up**
- Baby had passed away few days earlier
- Transferred for higher level care

![Graph showing HCT (%) over time from admission](image)
Acknowledgements

• Bimpe Adesina, MD

• Monica Pagano, MD

• Theresa Nester, MD
Thank you!
Number of fatalities reported to the FDA (2011-2015)

Includes reports of DHTR and Hyperhemolysis Syndrome with no new or additional antibodies.

Common clinical findings during DHTR in Sickle Cell Disease

<table>
<thead>
<tr>
<th>Finding</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Hemoglobinuria/dark urine</td>
<td>96%</td>
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<tr>
<td>Pain</td>
<td>89%</td>
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<tr>
<td>Fever</td>
<td>64%</td>
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<tr>
<td>Anemia signs</td>
<td>44%</td>
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Delayed Hemolytic Transfusion Reaction presents 1 to 21 days after transfusion

- **Good outcome**
  - Persistence of transfused RBCs
  - HbA% ++
  - Total Hb ++

- **Mild Outcome**
  - Destruction of transfused RBCs
  - HbA% ±
  - Total Hb ±
  - LDH +

- **Severe Outcome**
  - Destruction of transfused and autologous RBCs
  - Hyperhemolysis
  - HbA% none
  - Total Hb decreased from pre-transfusion
  - Reticulocytopenia
  - LDH +++

Adapted from France Pirenne, AABB 2016
### Risk of Alloimmunization

#### Donor Factors
- Age
- Sex
- Ethnicity
- Inflammation status of donor

#### Recipient Factors
- Age
- Sex
- Ethnicity
- Antigen recognition
- Antigen exposure
- Disease state
- Immune status and Inflammation

#### Unit Factors
- RBC antigen immunogenicity
- Storage lesion
- Modification:
  - leukoreduction
  - irradiation

Adapted from Jeanne Hendrickson, Yale University
Nucleic acid blood grouping for transfusion in SCD

• Problems with alloimmunization
  – Risk of dhtr
  – Shorten rbc survival
  – Complicate crossmatching
  – Multiple antibodies hard to match – also if develop ab to high prevalence or low prevalence antigens

• Error rate of serologic typing 1.1% (66/ or 6360 discrepancies and 64/66 repeat serology agreed) genotype highly reliable (Casas Transfusion 2015)
Nucleic acid blood grouping for transfusion in SCD

- As high as 1 in 20 aa are heterozygote have trait
- 1 in 400-500 homozygous for HbSS
- RBC antigens: 352 antigen, 45 genes ~2000 alleles
- Standard C,E,K matched RBCs
- Using D neg donors for D pos recipients to match C,E, and K so need large donor base
  - 26% D+, C-, E-, K-, Fya-, Fyb-
  - 2% Caucasian D+, C-, E-
- Stop trial, SIT trial, Philadelphia Chou analyze alloimmunization receiving C, E, K matched
- Blue tie tag program self-identified African americans designate donation to SCD patient
- Chou and Westhoff, Blood 2013, no anti-K but still large number Rh antibodies -2/3 against Rh, antibodies to low frequency antigens more common in African americans (Joa, Goa, V)
- Association with hemolysis 1/3 had DHTK

David Friedman, CHOP
• Matzinger science 2002 296 301-5 showing disease state affecting immune response
• Inflammation and RBC alloimmunization
Rh allele frequencies in Caucasians versus African Americans

- Allele Frequencies
  - R1 (D+, C+, E-) 0.42 0.17
  - Ro (D+, C-, E-) 0.04 0.42
  - r (D-C-E-) 0.37 0.26
## Predicted Phenotype from Red Cell Genomics Report

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Follow-up

- 10/15/16: Hgb 3, HCT 9%, LDH >4300
- 10/17/16: H/H 6.3/17, LDH 2288, retic 284
- 10/18/16: H/H 5.8/15.9, LDH 1924, retic 289, hapto <1
- 10/19/16: H/H 5.6/15.9
- 10/20/16: HCT 16.7, Hgb 6.0, LDH 1384

- Prednisone 1 mg/kg
- IVIG 400 mg/kg/Day for 5 days total
- Recommend transfuse only if Hct<14 or patient symptomatic
Proposal: Two forms of Hyperhemolysis Syndrome

1. Acute
   - DAT negative
   - No new red cell alloantibodies or only non-clinically significant antibodies

2. Delayed
   - DAT positive
   - Presence of red cell alloantibody formation
Initial Case History at Bloodworks Immunohematology Reference Lab

• 29 year old female

• Prior type and screen on 10/5/16:
  - B positive; antibody screen: negative

• Transfused 2 units of RBCs on 10/7/16 for reported HCT 18%

• Admitted to Overlake hospital 10/14/16 9:30pm, Hgb 5.9, HCT 17%

• 2 units of RBCs ordered

• Admission type and screen on 10/14/16:
  - B positive; antibody screen: positive (anti-C, anti-S, anti-M)

  Are you worried about these results?