Blood Safety: Sickle Cell Disease and Stroke Management

Margo Rollins, MD
Assistant Professor of Pathology
Emory University SOM
Assistant Medical Director for Tissue, Transfusion & Apheresis
Children’s Healthcare of Atlanta
Pediatric Sickle Cell Mini Symposium
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Disclosures

• None
Please remember…

• You are learning Transfusion Medicine in 60 minutes
  – I took:
    • 4 years of medical school
    • 3 years of residency
    • 4 years of fellowship (Peds Heme-Onc AND Transfusion Medicine)

• Your baseline knowledge is likely more than most physicians!
Objectives

• Component acquisition, storage, and modification
• Major and minor antigens (ABO blood groups and more)
• Pre-transfusion testing
• Complications of transfusions
• Transfusion and stroke management in SCD
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Component Therapy

- Give the patient ONLY what is needed
- Efficient use of blood supply
- One unit of whole blood can be shared with many patients

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Directed Donor Units

• Donor and recipient blood types should be drawn to ensure potential compatibility
• Not as safe as the general blood supply
• Must all be irradiated to prevent transfusion associated GVHD
• Cannot be crossed over into the general blood bank inventory if not needed
## Component Storage

### Blood Products/Storage Conditions

1. **Anticoagulant (AC)/preservative solutions (PS):** backbone of citrate, phosphate, dextrose and adenine (CPDA) → anticoagulate blood components, provide cellular energy for ATP production, and raw materials for anaerobic metabolism.

2. **AC/PS that RBC unit is stored in determines the shelf life of that unit.**

3. **Additive solution RBC units (ie. AS-1 or AS-3):** contain additional preservative elements causing the volume that can be transfused to a neonate to be limited and not to exceed > 15 – 20 ml/kg total per dose.
# Component Storage

<table>
<thead>
<tr>
<th>Blood Component</th>
<th>Storage Temp.</th>
<th>Storage Duration</th>
<th>Storage Medium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Blood</td>
<td>3-6 °C</td>
<td>35 days</td>
<td>CPDA-1</td>
</tr>
<tr>
<td>Packed Red Blood Cells</td>
<td>3-6 °C</td>
<td>35 days</td>
<td>CPDA-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>42 days</td>
<td>Additive Solution (AS)</td>
</tr>
<tr>
<td>Platelets</td>
<td>22 °C</td>
<td>5 days</td>
<td>Gas Exchange w/ constant agitation</td>
</tr>
<tr>
<td>FFP, FP24 and Cryoprecipitate</td>
<td>-18 °C</td>
<td>1 year</td>
<td>Freeze within 8 – 24hrs after collection</td>
</tr>
<tr>
<td></td>
<td>thawed</td>
<td>24 hrs</td>
<td></td>
</tr>
</tbody>
</table>
RBC Modifications

• So many choices, so little time!
  – Leukoreduced
  – Irradiated
  – Washed
Leukoreduction

- 3 log reduction of WBCs
- Decreases febrile transfusion reactions, viral transmission
- 80% of products transfused in the US are leukoreduced, **pre-storage**
- ALL blood supplied to CHOA is prestorage leukoreduced
Irradiation

- Prevents transfusion associated GVHD in immunocompromised pts by making T-cells in transfused blood incapable of proliferating
- Not necessary in patients with SCD UNLESS prepping for or management during BMT
Washing

- Removes plasma proteins and antibodies
- Indicated for pts with IgA deficiency + anaphylaxis or an anaphylactic reaction to prior blood products
- Removes potassium in older units
- Causes hemolysis of RBCs
- Must be used within 24 hours of washing
Objectives

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ABO Blood Group

- A and/or B antigens on RBCs

<table>
<thead>
<tr>
<th>Donor %</th>
<th>RBCs</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>44%</td>
<td>A</td>
<td>Anti-B IgM</td>
</tr>
<tr>
<td>4+4=8%</td>
<td>B</td>
<td>Anti-A IgM</td>
</tr>
<tr>
<td>4%</td>
<td>AB</td>
<td>No anti-A or B antibody</td>
</tr>
<tr>
<td>44%</td>
<td>O</td>
<td>Anti-A,B IgG</td>
</tr>
</tbody>
</table>
ABO Antibodies (Ab)

• Individuals produce Ab directed toward the A or B antigen(s) absent from their cells
• Anti-A and –B can generally be detected in serum after the first few months of life
  – Hypothesis= ABO Ab produced in response to A- and B- like antigens present in environment (bacteria)
• Ab production reaches the adult level at 5-10 years of age
Rh (Rhesus)

- Rh(D) is the most immunogenic RBC antigen
- Vast majority of people in the US are Rh(D) positive:
  - 85% of non-Hispanic whites
  - 93% of Hispanics and blacks
  - 99% of Asians
- If possible, provide Rh(D) negative products to Rh(D) negative girls and women of childbearing age
## ABO/Rh Distribution of Donor Population

<table>
<thead>
<tr>
<th>ABO/Rh status</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A+</td>
<td>31</td>
</tr>
<tr>
<td>A−</td>
<td>6</td>
</tr>
<tr>
<td>B+</td>
<td>9</td>
</tr>
<tr>
<td>B−</td>
<td>2</td>
</tr>
<tr>
<td>O+</td>
<td>39</td>
</tr>
<tr>
<td>O−</td>
<td>9</td>
</tr>
<tr>
<td>AB+</td>
<td>3</td>
</tr>
<tr>
<td>AB−</td>
<td>1</td>
</tr>
</tbody>
</table>

[www.aabb.org/resources/bct/Pages/bloodfaq.aspx](http://www.aabb.org/resources/bct/Pages/bloodfaq.aspx)
Phenotypic Matching

• Done to decrease the risk of RBC alloimmunization in patients with SCD
  – C,E,K phenotypic matching for all SCD
  – Extension to Fy^a and Jk^b in previously alloimmunized patients
<table>
<thead>
<tr>
<th>Antigen</th>
<th>Caucasians</th>
<th>AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>85</td>
<td>92</td>
</tr>
<tr>
<td>C</td>
<td>68</td>
<td>27</td>
</tr>
<tr>
<td>c</td>
<td>80</td>
<td>96</td>
</tr>
<tr>
<td>E</td>
<td>29</td>
<td>22</td>
</tr>
<tr>
<td>e</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>K</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>k</td>
<td>99.8</td>
<td>99.9</td>
</tr>
<tr>
<td>Jk^a</td>
<td>77</td>
<td>91</td>
</tr>
<tr>
<td>Jk^b</td>
<td>72</td>
<td>43</td>
</tr>
<tr>
<td>Fy^a</td>
<td>66</td>
<td>10</td>
</tr>
<tr>
<td>Fy^b</td>
<td>83</td>
<td>23</td>
</tr>
<tr>
<td>M</td>
<td>78</td>
<td>70</td>
</tr>
<tr>
<td>N</td>
<td>72</td>
<td>74</td>
</tr>
<tr>
<td>S</td>
<td>55</td>
<td>31</td>
</tr>
<tr>
<td>s</td>
<td>89</td>
<td>97</td>
</tr>
<tr>
<td>Le^a</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>Le^b</td>
<td>72</td>
<td>55</td>
</tr>
</tbody>
</table>
RBC Membrane Antigens

Photos removed for copyright compliance
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## Pre-Transfusion Testing

### Testing Requirements

1. Type and screen- testing a patient’s ABO and Rh (D) blood type and an indirect antiglobulin test with patient plasma/serum mixed with 2-4 reagent red blood cells.

2. The purpose of a type and screen- determine if the patient has unexpected clinically significant (may cause a hemolysis) antibodies present in their plasma/serum.

3. Type and crossmatch- type and screen in addition to mixing the patient’s plasma/serum with red blood cells of the donor unit to be transfused.

4. Crossmatching a unit of red blood cells does not imply that it will definitely be transfused, but that it is highly likely.
# Type and Screen

- **Type** = A/B/O, Rh
- **Screen** = Screening pt’s PLASMA for unknown antibodies
  - Honored for 3 days

<table>
<thead>
<tr>
<th>CELL</th>
<th>Rh</th>
<th>MNS</th>
<th>Lutheran</th>
<th>P</th>
<th>Lewis</th>
<th>Kell</th>
<th>Duffy</th>
<th>Kidd</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1R1-29</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>R2R2-45</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>rr-86</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>+</td>
</tr>
</tbody>
</table>
Ab Screening Methods

- **Tube**
  - Traditional

- **Gel**
  - Sensitive

- **Solid Phase**
  - Very sensitive
DAT (Coombs)

- Used to detect anti-RBC antibodies bound in vivo
- Washed patient RBCs are mixed with anti-human IgG (Coombs reagent)
  - Coombs reagent binds to IgG or C3 adherent to the RBC surface, leading to RBC agglutination
DAT: Direct Anti-globulin Test

- Anti-RBC Ab
- Complement

+ anti-IgG/complement

neg → pos → neg
Causes of a Positive DAT (IgG)

• **Autoantibodies** against an intrinsic RBC antigen (AIHA)
• **Alloantibodies** bound to circulating antigen positive donor cells
• Antibodies to drug (PCN, Cephalosporins)
• Up to 30% of hospitalized adults may have a positive DAT, with no evidence of hemolysis
Fate of Antibody-Coated RBCs

Photos removed for copyright compliance
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**Transfusion Risks Over Time**

**FIGURE 66.1** Comparison of transfusion risks and their evolution over time. HBV hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PLTs, platelets; RBCs, red blood cells; TRALI = transfusion related acute lung injury; From AuBuchon JP. (2004). Emily Cooley Memorial Award. Managing change to improve transfusion safety. Transfusion 44, 1377–1383.

Hillyer, Shaz, Zimring, Abshire. Transfusion Medicine and Hemostasis, 2009
# Adverse Effects of Transfusion

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Non-infectious</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Viral</td>
<td>• Hemolytic reactions</td>
</tr>
<tr>
<td>• HIV-1/2</td>
<td>• Acute or Delayed</td>
</tr>
<tr>
<td>• HBV</td>
<td>• Febrile non-hemolytic reactions</td>
</tr>
<tr>
<td>• HCV</td>
<td>• Allergic Reactions</td>
</tr>
<tr>
<td>• HTLV-I/II</td>
<td>• Urticarial only (aka. Hives only)</td>
</tr>
<tr>
<td>• CMV</td>
<td>• Anaphylactic</td>
</tr>
<tr>
<td>• Bacterial</td>
<td>• Transfusion Associated Volume Overload (TACO)</td>
</tr>
<tr>
<td></td>
<td>• Transfusion Related Acute Lung Injury (TRALI)</td>
</tr>
<tr>
<td></td>
<td>• Transfusion Associated Graft Versus Host Disease</td>
</tr>
</tbody>
</table>
Transfusion Transmitted Disease

## Current Estimated Residual Risk of Some Transfusion-Transmissible Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Risk Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV I/II</td>
<td>1:3,000,000 (ID-NAT)</td>
</tr>
<tr>
<td>HCV</td>
<td>1:2,300,000 (ID-NAT)</td>
</tr>
<tr>
<td>HBV</td>
<td>1:410,000 (ID-NAT)</td>
</tr>
<tr>
<td>Parovirus</td>
<td>1:40,000</td>
</tr>
<tr>
<td>T. Cruzi</td>
<td>1:42,000</td>
</tr>
<tr>
<td>Malaria</td>
<td>&lt; 1:1,000,000</td>
</tr>
</tbody>
</table>
“Window Period” Donations and HIV Risk

HIV Window Period

Infection with HIV  Becomes infectious as a donor  HIV RNA  p24 antigen  HIV DNA  HIV antibody 1995  HIV antibody 1990

old window = 22 days
new window = 16 days
5-10 days
10 - 13 days
23 days
45 days

SHORT

Aflac Cancer and Blood Disorders Center
## Bacterial Contaminants

<table>
<thead>
<tr>
<th>Product</th>
<th>Storage</th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>pRBC</td>
<td>4°C</td>
<td>Y. enterocolitica</td>
<td>P. putida</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P. fluorescens</td>
<td>T. pallidum</td>
</tr>
<tr>
<td>Plts</td>
<td>24°C</td>
<td>S. epidermidis</td>
<td>S. marcescens</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>S. aureus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B. cereus</td>
</tr>
<tr>
<td>HPC</td>
<td>-70°C</td>
<td>S. epidermidis Propionibacterium</td>
<td>S. aureus Pseudomonas sp</td>
</tr>
</tbody>
</table>
Septic Transfusion Reaction

• Bacterial contamination is the #1 infectious risk from transfusion
• May present with **rapid** onset of high fever, rigors, n/v, abdominal cramping, shock
• Platelets: 1/3000
  – Skin flora (i.e. Staph)
• RBCs: 1/250,000
  – Cold loving organisms (i.e. Yersinia, Citrobacter, E. coli, Pseudomonas)
Hemolytic Transfusion Reactions

- Usually Ab-mediated

- Acute Hemolytic Transfusion Reaction (AHTR): intravascular hemolysis
  - ABO incompatibility (PP₁, Pk, Vel, Lew, Jk)
  - Within 24 hours of tx (usually mins)

- Delayed Hemolytic Transfusion Reaction (DHTR): extravascular hemolysis
  - Primary: New Ab; weeks post-tx
  - Anamnestic: ↑ Ab titer; > 3 days post-tx
    - Kidd (Jk), Duffy (Fy) blood group systems
Acute Hemolytic Transfusion Reaction (AHTR)

• Incompatible red blood cells or plasma transfused (primarily ABO-incompatibility)
• Most often due to clerical errors
  – Mistakes in patient and/or sample identification
• Intravascular destruction (within 24 hours)
• Hemolysis, hypotension, shock, DIC, ARF
• Number of ABO incompatible transfusions: 1/14,000- 1/38,000
Delayed Hemolytic Transfusion Reaction (DHTR)

- Gradual \( \downarrow \) Hct; usually extravascular hemolysis b/c complement not activated

- Anamnestic: antibodies can fall to levels undetectable by Ab Screen/X-Match:
  - Kidd (Jk\(^a\), Jk\(^b\))
  - Rh (E, C)

- Fever, mild jaundice

- 26 deaths from 1976-1985 (FDA)
Febrile Non-Hemolytic Transfusion Reaction (FNHTR)

- Diagnosis of exclusion for Fever (1°C)
- Most common tx rx: 0.5-2% of transfusions
- Can manage with Tylenol (325-650 mg)
- Premedication:
  - for repeated FNHTRs (10-15%) and/or FNHTRs with LR units
- Leukoreduction of cellular blood components has greatly decreased incidence!
Allergic Reactions

• Mild urticaria (the **ONLY** reaction in which transfusion can be restarted)
  – 0.1-0.3% RBC
  – hives, urticaria, pruritis, erythema, flushing
  – IgE response to soluble proteins in donor plasma, release histamine, leukotrienes, prostaglandins

• Anaphylactic/anaphylactoid
  – 1:20-50,000
  – bronchospasm, hypotension, shock, cardiovascular instability, nausea, cramps
  – IgA deficient pts with high-titer anti-IgA
# Methodologies to reduce adverse reactions

<table>
<thead>
<tr>
<th></th>
<th>Screening</th>
<th>Medicate</th>
<th>LR</th>
<th>$\gamma$-irrad.</th>
<th>Washing</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV, HBV, HCV, HTLV</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV</td>
<td>+++</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic</td>
<td></td>
<td>+++</td>
<td></td>
<td></td>
<td>+++</td>
</tr>
<tr>
<td>FNHTR</td>
<td></td>
<td>+++</td>
<td>+++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alloimm.</td>
<td></td>
<td></td>
<td>+++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TA-GVHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+++</td>
</tr>
</tbody>
</table>
## Alloimmunization Rates

<table>
<thead>
<tr>
<th>Population</th>
<th>RBC Alloimmunization</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCD</td>
<td>18-47%</td>
</tr>
<tr>
<td>(Pediatric: 18-30%)</td>
<td></td>
</tr>
<tr>
<td>Thalassemia</td>
<td>5-19%</td>
</tr>
<tr>
<td>General</td>
<td>0.2% - 2.8%</td>
</tr>
</tbody>
</table>

Complications of Alloimmunization

• **Inventory / Cost:** Difficulty or impossibility of finding compatible RBC units

• **Autoantibodies:** Strong association reported between autoantibody formation and the presence of alloantibodies.

• **Ab-Negative DHTR:** Process attributed to antibody-independent macrophage activation.

• **DHTR Treatment:** Controversial; exact mechanisms remain unclear
  – IVIG / Steroids / Rituxan
  – Avoidance of RBC transfusion

• **Future BMT Implications:** May affect HSCT decisions for heavily alloimmunized

Iron Overload & Organ Dysfunction: SCD vs β Thalassemia

Comparison of organ dysfunction in transfused patients with SCD or β Thalassemia

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>β Thalassemia (N = 30)</th>
<th>SCD (N = 43)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>18.37 ± 2.1</td>
<td>14.8 ± 1.0</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of chronic transfusions (years)</td>
<td>12.2 ± 1.8</td>
<td>6.0 ± 0.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Serum ferritin (mg/mL)</td>
<td>2,122 ± 289</td>
<td>2,916 ± 233</td>
<td>0.04</td>
</tr>
<tr>
<td>Liver iron (mg/g dry wt)</td>
<td>14.79 ± 2.15</td>
<td>14.33 ± 1.38</td>
<td>NS</td>
</tr>
<tr>
<td>Organ dysfunction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>20%</td>
<td>0</td>
<td>0.002</td>
</tr>
<tr>
<td>Growth delay</td>
<td>27%</td>
<td>9%</td>
<td>NS</td>
</tr>
<tr>
<td>Endocrine disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7%</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>7%</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Gonadal failure</td>
<td>33%</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Liver Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>33%</td>
<td>2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormal ALT (&gt;65 U/L)</td>
<td>37%</td>
<td>7%</td>
<td>0.003</td>
</tr>
<tr>
<td>Abnormal fibrosis score (&gt;0)</td>
<td>81%</td>
<td>39%</td>
<td></td>
</tr>
</tbody>
</table>

Objectives

• Component acquisition, storage, and modification
• Major and minor antigens (ABO blood groups and more)
• Pre-transfusion testing
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Sickle Cell Disease

Source: University of Louisville

By Steve Reed, The Courier-journal
Pathophysiology of Sickling

- Polymerization
- Membrane changes
- Intravascular hemolysis
- Adhesion
- Inflammation (increased WBC)
- Changes in platelet function and coagulation
  - Complex vasculopathy
Manifestations of Sickle Cell Disease

- Chronic hemolytic anemia
  - Jaundice, pallor, fatigue
  - Cholelithiasis (bilirubinate)
  - Endothelial dysfunction

- Acute complications
  - Pain, priapism, stroke
  - Acute chest syndrome
  - Splenic sequestration

- Chronic organ damage
  - Spleen, brain
  - Kidneys, lung, bones, eyes
CNS Complications

- Incidence 7-11% in the first 20 years (highest rate 5-10yo)
- In children: Infarction >hemorrhage (Vs Adults)
- Most common underlying lesion: Intracranial Arterial Stenosis/Obstruction (Internal carotid, MCA, ACA)
- Studies:
  - CT scan best initial test
  - MRI including arterial and venous studies
- Recommendation by NHLBI for TCD screening
  - ALL SS pts 2-16 yrs: annual screening TCD US
  - >16yrs with poor school performance or other risk factor: MRI/TCD US
TCD and Stroke Risk Detection

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Sickle Cell and Stroke

• Exchange Transfusion: limit progression of CNS injury (Goal to decrease HbS <30%, keep HCT=30)
• Maintenance transfusions: stroke or abnormal TCD
  – keeping HbS<30% lowers recurrence risk to10%
• Mortality if untreated 20%
• Recurrence (without transfusions) 70% in 3yrs
Options for Chronic Transfusion Therapy (CTT)

- **Goal:** Improve O2 carrying capacity and ↓ % of Hg-S carrying RBCs
- **Simple Transfusion:**
  - Sequestration crisis
  - Aplastic crisis
  - ACS
  - In preparation for surgery/general anesthesia
- **Exchange Transfusion:** Rapid reduction of Hb S (target Hb S<30%, HCT=30%)
  - Stroke
  - Severe ACS or multiorgan failure
  - 60-80% reduction in sickle cells by double volume exchange
Role of Chronic Transfusion

• Chronic transfusions (< 30% S) - Most common indications in children:
  – Clinical stroke
  – Abnormal TCD
  – Recurrent ACS
  – Splenic sequestration
  – Severe recurrent VOC

• Risks: Fe overload, Allo/auto-antibodies
Thank you!

• Questions???