Transfusion Reactions

Lawrence B. Fialkow, D.O.
Medical Director
American Red Cross
East Division Blood Services

The need is constant.
The gratification is instant.
Give blood.

Objectives:

- Recognize the initial signs and symptoms of a transfusion reaction
- Understand the basic work up for a transfusion reaction
- Recognize specific reactions:
  - Acute hemolytic transfusion reaction
  - Bacterial contamination/infection
  - Transfusion related acute lung injury (TRALI)
  - Transfusion associated circulatory overload (TACO)
History of Blood Transfusions

- 1667
  - Lamb to human transfusion
- 1816
  - 1st human to human transfusion
- 1900
  - Discovery of the first blood group (ABO)
- 1907
  - Pre-transfusion cross-match
- 1915
  - 1st anticoagulant solution
- 1930's
  - Blood banks
- 1940's
  - Blood fractionation
- 1950's
  - Plastic blood bags
- 1960's
  - Hemodialysis
- 1970's
  - Hepatitis B testing
- 1980's
  - HIV testing
- 1990's
  - Hepatitis C testing
- 2000's
  - "Zero risk" blood (NAT testing)

"Zero Risk" Blood

Rate of dying from non-transfusion cause

Perkins et al. Transfusion 2010;50:2080
Transfusion-Related Fatalities

During FY2012, 74 potential transfusion-related recipient fatalities were reported to FDA:

- 38 (51%) were transfusion-related
- 27 (36%) were cases in which transfusion could not be ruled out as the cause of the fatality
- 9 (12%) of the fatalities were unrelated to the transfusion
Transfusion Reactions

- Recognizing signs and symptoms of adverse reactions, with timely lab evaluation, is essential due to the potentially life-threatening nature of acute transfusion reactions
- Assume all reactions are hemolytic until proven otherwise

Basics

- STOP THE TRANSFUSION!!!
- TREAT SYMPTOMS
  - Keep the line open with 0.9% normal saline
  - Monitor vital signs and symptoms
- Report the reaction to the physician, transfusion service, and blood center
- Collect appropriate specimens and send to laboratory
- Return blood bag with administration tubing set, all attached bags to Blood Bank

Initial Laboratory Evaluation

- Blood Bank
  - Immediate visual checks for hemolysis
  - Direct antiglobulin test (DAT)
  - Clerical check
  - Repeat ABO/Rh of patient
  - Examine blood bag, administration set, IV fluid bags
Initial Laboratory Evaluation

- Immediate visual check for hemolysis
  - Can detect free hemoglobin with lysis of as little as 10 cc red cells

- If red/dark urine – send next fresh urine sample
  - Check for hemoglobinuria
- Collect other samples per protocol, physician’s orders
Direct Antiglobulin Test

- Compare to pre-transfusion DAT:
- Positive DAT
  - Allantibody coated RBCs
  - Autoantibodies
  - Drug antibodies
- Negative DAT
  - Non-immune mediated hemolysis
  - Transfused cells already destroyed
  - Inensitive test – small number of antibody coated RBCs may be missed

Positive DAT

- Always rule out an acute hemolytic reaction:
  - Repeat pre/post sample ABO Rh
  - Repeat pre/post antibody screen
  - Repeat crossmatch of units with pre/post sample
  - Additional tests for hemolysis
    - Bilirubin
    - Haptoglobin
    - LDH

Negative DAT

- Usually/o acute hemolysis
  - If significant temp increase
    - F hottle nonhemolytic vs. sepsis
    - Unit and patient gram stains & cultures
  - If respiratory symptoms
    - Chest X-Ray & ABG
    - TRALI vs. TACO
      - Oxygen support vs. diuresis
Acute Hemolytic Transfusion Reaction

- Acute hemolysis of transfused red cells due to presence of preformed antibody
- Usually due to ABO incompatible RBCs
- Majority due to clerical error
  - Phlebotomy/ordering – 10%
  - Blood bank – 33%
  - Transfusion administration – 57%

Acute Hemolytic

- Usually occurs early in transfusion
- Severity related to amount of blood transfused: value of early recognition
  - May be clinically mild
  - Fatality rate 15-20%
- Can be intravascular or extravascular
  - ABO typically intravascular
Acute Hemolytic-Causes

- Immune reaction: ABO or other antigens
- Non-immune etiologies
  - Concurrent medications
  - Antimicrobials
  - Tube/blood set problems
  - Use of blood warmers/infusion pumps
    - Temperature, flow rate, needle size
  - Improper blood storage
  - Incompatible solutions
    - Hyper or hypotonic fluids
  - Heat (>50°C) or cold (freezing)

Acute Hemolytic-Symptoms

- Fever (usually > 2°C rise)
- Chills
- Nausea/vomiting
- Pain at IV site, back pain, chest pain
- Dyspnea
  - Sense of impending doom/anxiety
- Hypotension/shock
- Diffuse bleeding - DIC
- Renal failure

Acute Hemolytic-Laboratory

- Hemoglobinemia
- Positive DAT
  - Eluates demonstrate anti-A or anti-B
  - May be negative if all donor RBC hemolyzed
- Coagulopathy - DIC
- ↑ indirect bil, ↑ LDH, ↓ haptoglobin
- Hemoglobinuria
- RBC abnormalities
  - Schistocytes (intravascular)
  - Spherocytes (extravascular)
Acute Hemolytic Laboratory

Acute Hemolytic Transfusion Reaction vs. Other

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Rate</th>
<th>Rate/2,000,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dying from non-transfusion cause</td>
<td>6 in 1000</td>
<td>12,000</td>
</tr>
<tr>
<td>AHTR</td>
<td>1 in 25,000</td>
<td>80</td>
</tr>
<tr>
<td>HBV</td>
<td>1 in 200,000</td>
<td>10</td>
</tr>
<tr>
<td>HTLV</td>
<td>1 in 650,000</td>
<td>3</td>
</tr>
<tr>
<td>HIV/HCV</td>
<td>1 in 2,000,000</td>
<td>1</td>
</tr>
</tbody>
</table>

AHTR Fatalities, 2001-2012
Acute Hemolytic-Treatment

- **Renal function:**
  - Vasodilation to increase renal blood flow (dopamine)
  - Alkaline urine (pH>7.5) to keep hemoglobin soluble and prevent deposition with tubular damage
  - Prevent acute tubular necrosis with hydration and diuretics (mannitol or furosemide)
- **Hypotension:**
  - Fluids, pressors
- **DIC:**
  - Blood components if bleeding
- **RBC exchange** – severe reaction

---

Bacterial Contamination/Sepsis

- #1 infectious risk from transfusions
- **Usually platelet products**
  - Stored at RT for 5 days
  - Up to 1 in 750 to 1,500 platelet products are contaminated
  - RBC rate - 1 in 30,000 to 40,000
- **Rates of septic events**
  - Platelets - 1 in 10,000 (fail 1 in 300,000)
  - RBC - 1 in 1,000,000
Bacterial Contamination of Platelets

- Gram + cocci
- Staph aureus
- Staph epidermidis
- Strep
- Bacillus
- Klebsiella
- Serratia
- Salmonella
- Entamoeba
- E. coli
- Pseudomonas
- P. mirabilis

Bacterial Contamination of RBCs

- Yersinia enterocolitica
- Pseudomonas spp.
- Entamoeba spp.
- Serratia
- Staph aureus
- C. perfringens
- B. anthracis
- Entercoccus n.

Bacterial Contamination/Sepsis

- Reaction severity correlates with bacterial concentration (significant > 10^5 CFU)
- Symptoms usually occur early in transfusion
  - Fever
  - Rigors/chills
  - Hypotension
  - Nausea/vomiting
  - Shortness of breath
- RBC reactions tend to be more severe
  - Endotoxins from gram neg organisms
Rough Estimates of Clinical Reactions to Contaminated Platelets

- Transfusion of bacterial contaminated components: 1: 750-1,500
- Febrile reactions: 1: 5-10,000
- Sepsis: 1: 100,000
- Death: 1: 500,000

Fatalities by Blood Product

- Bacterial Contamination/Sepsis
  - Diagnosis:
    - Gram stain positive in only 20% of cases
    - Culture of unit and recipient
  - Treatment:
    - Broad spectrum antibiotics
    - Therapy for shock:
      - Vasopressors
      - Fluid support
      - Ventilation
Bacterial Contamination-Prevention

• Blood collection facility:
  – Health history screening of donors
  – Careful selection of phlebotomy sites
    • Avoid areas of scarring, dimpling
  – Thorough cleaning of phlebotomy site
  – Diversion of initial volume w/skin plug
  – Bacterial screening of platelet products

Bacterial Contamination-Prevention

• Transfusing facility:
  – Inspection of units prior to transfusion
    • Cloudy/discolored product
    • Particles
  – Transfuse within 4 hours/prior to expiration
  – Reduce shelf life from 7 to 5 days
  – Pathogen inactivation technology?

Bacterial Contamination of Platelets

Bad

Good
Bacterial Contamination of RBCs

• Very Bad
• Good

Transfusion Related Acute Lung Injury

- TRALI definition:
  - New onset acute lung injury during or within 6 hrs of transfusion
  - PaO2/FiO2 < 300
  - Arterial O2 sat < 90% on RA
  - Bilateral infiltrates on CXR
  - No alternative ALI risk factors (“possible” TRALI)

- #1 cause of transfusion-related fatalities reported to FDA
- Usually associated with plasma products
TRALI: Two Hit Hypothesis

- 1st – recipient neutrophils line pulmonary vasculature
- 2nd – anti-HLA or anti-neutrophil antibodies
  (90% donor/10% recipient)
  - OR -
  Biologic response modifiers (lipids, etc)
  in blood product
  Activate neutrophils
  - Vascular permeability
  - Pulmonary edema

TRALI: Radiographic Findings

Figure 1 – Pre and post-emergency RT of a patient with TRALI. Bilateral lung infiltrate with pulmonary edema is an essential feature for the clinical diagnosis of TRALI. Radiographic discrepancies can be seen in the first hours after transfusion, with progression of the wedge and interstitial infiltrate throughout the lung. Radiographic changes used to be more specific than the results of physical examinations. TRALI translates to ‘related acquire lung injury’

TRALI: Diagnosis of Exclusion

- 1 - Vital signs
  - Hypotension
  - Respiratory symptoms
  - Pyrexia
  - Pulmonary infiltrate
  - Sputum production

- 2 - Hemodynamic
  - Hypotension
  - Reduced central venous pressure

- 3 - Hematologic
  - Leukocytosis
  - Decreased hematocrit

- 4 - Clinical
  - Cardiac arrest
  - Resuscitation

- 5 - Nonspecific
  - Acute大众 disease
  - Severe sepsis

- 6 - No other cause
  - TRALI

www.frca.co.uk
TRALI Treatment

- Supportive
  - Oxygen
  - Intubation
  - Diuretics are not indicated

- Most will improve within 48-96 hours with prompt and aggressive respiratory support

- 10-20% mortality rate

Fatalities Reported to FDA: 2005-2010

Fatalities Reported to FDA: 2008-2012
TRALI Fatalities: 2002-2012

TRALI Fatalities by Product: 2005-2010

TRALI Fatalities by Product: 2008-2012
TRALI-Data

- HLA antibody prevalence:
  - Males:
    - Non-transfused 1.0% vs. transfused 1.7%
  - Females:
    - 17.3% all donors
    - 24.4% with previous pregnancy
      - 1.7% (zero pregnancies)
      - 11.2% (one)
      - 22.5% (two)
      - 27.5% (three)
      - 32.2% (4+)

Triulzi et al, Transfusion, 2009

TRALI-Prevention

- Appropriate use of blood products
- Reduce exposure
  - Use of male donors for high plasma volume products
    - ARC plasma is >95% male donors
    - ARC SDP
      - Males recruited as new donors; testing of
      - Female donors tested for HLA antibodies
- Defer donors implicated in TRALI
Transfusion Associated Circulatory Overload

- **TACO Etiology:**
  - Cardiovascular inability to compensate for the increased volume associated with transfusion
  - **TOO MUCH FLUID!!!**
- **Vulnerable patients:**
  - Infants
  - Elderly
  - Positive fluid balance pretransfusion
  - Cardiac or renal compromise
  - Massive blood transfusion

TACO-Symptoms

- Dyspnea
- Non-productive cough
- Pulmonary edema
- CHF
- Hypertension
- Tachycardia

TACO-Laboratory

- B-type natriuretic peptide
  - Synthesised and secreted by ventricular myocardium in response to volume and pressure distension
  - Sensitivity of 81% & specificity of 89% for diagnosis of TACO
- Radiographic findings
  - Pulmonary vascular congestion
  - Alveolar and interstitial edema
  - **Cardiomegaly**
  - Pleural effusions
TACO Treatment

- **Diuretics**
- Oxygen
- If severe
  - Therapeutic phlebotomy
- Future transfusions
  - Slow rate - 1ml/kg/hr
  - Use sequential half-units
  - Prophylactic diuretics may be indicated

Conclusion: Keep Recipient Safe

- Be able to recognize signs & symptoms of potential transfusion reactions
- Provide immediate treatment
- Examine all the evidence to make the correct diagnosis
- Report the potential reaction:
  - Submit transfusion reaction workup
  - Consult with Blood Bank
  - Notify Blood Center when appropriate

The End