TRALI, TRIM, TACO and Others: Adverse Blood Transfusion Reactions In Surgical Patients and the Influence on Mortality

M. J. Osgood
5/15/13
Background

• Adverse events following transfusion – difficult to estimate, probably ~20%
• 0.5% of adverse events are serious
• Most common:
  – Alloimmunization to leukocytes or platelets (~10%)
  – CMV seroconversion (~7%)
  – Alloimmunization to red blood cells (~1%)
Complications

- Immunologic
- Non-immunologic
Immunologic Complications

- **Immunologic Transfusion Reactions**
  - Red cell hemolysis → Antibodies in patient or donor
  - Febrile → White blood cells in component
  - TRALI → White blood cells or cytokines in components
  - Allergic → Plasma proteins in components
  - Anaphylactic → Plasma proteins (IgA) in components

- **Graft-versus-host disease** → Caused by viable lymphocytes

- **Immunization of Immune Modulation (TRIM)**
  - White cells → Febrile reaction; platelet refractoriness
  - Platelets → Febrile reaction; platelet refractoriness
  - Red cells → Hemolytic reaction
  - Graft acceptance → Caused by white cells
  - Cancer recurrence → Caused by white cells
  - Postoperative infection → Caused by white cells
Non-Immunologic Transfusion Reactions

• Disease Transmission
  – Viral → Caused by contaminated component
  – Bacterial → Caused by contaminated component
  – Parasitic → Caused by contaminated component

• Other adverse effects
  – Circulatory overload (TACO)
  – Citrate toxicity → Caused by citrate anticoagulant
  – Bleeding tendency → Massive transfusion
  – Electrolyte imbalance → May cause arrhythmia
  – Hemosiderosis → Caused by chronic transfusions
  – Embolism → Air or particles
  – Arrhythmia → Cold blood
  – Electrolyte imbalance → Citrate anticoagulant
  – Non-immunologic hemolysis → Improper storage
    Tranfused through small-bore needle
Hemolytic Transfusion Reaction

- Leading cause of transfusion-related deaths
- May be immediate or delayed (depends on type of pre-formed immunoglobulin present)
- Complement activation, cytokine release, activation of coagulation system by antigen-antibody complexes
- DIC, coagulopathy, oliguria, renal failure result
Delayed Hemolytic Transfusion Reaction

• No detectable red blood cell antibody present at time of compatibility testing
• Accelerated red blood cell destruction occurs after an interval during which an immune response to the transfused red cells occurs
• Delayed 24 hrs to 1 week after transfusion
• Most common symptom is decrease in hemoglobin after transfusion
• Uncommonly: hyperbilirurbinemia, oliguria
Febrile Nonhemolytic Transfusion Reactions

• 0.5-1% incidence
• Caused by leukocyte antibodies present in the patients that react with leukocytes present in the transfused PRBCs, PLTs
• Nonhemolytic
• Symptoms: chills, fever, headache, malaise, nausea, vomiting, and chest/back pain
• Self-limited
• May be prevented with use of leukocyte-reduced PRBCs, antipyretics
• Antipyretics are not recommended for routine use given the rarity of this condition
Allergic Reactions

- Most frequent transfusion reaction (~1-2%)
- Types: hives, respiratory symptoms, anaphylaxis
- Caused by IgE antibodies, histamine release from leukocytes stored in PRBCs
TRALI

• Clinical syndrome of acute onset pulmonary edema due to antibody-induced non-cardiogenic pulmonary edema

• 5-10% mortality; higher incidence in ventilated and surgical pts

• Incidence: 1/4,500 (likely higher; difficult to diagnose)

• Signs/Symptoms: fever, hypotension, tachypnea, dyspnea, diffuse pulmonary infiltrates on CXR, resembles non-cardiogenic pulmonary edema
Panel 1: Definition of transfusion-related acute lung injury (TRALI)

Suspected TRALI
- Acute onset within 6 h of blood transfusion
- \( \text{PaO}_2/\text{FiO}_2 < 300 \text{ mm Hg, or worsening of P to F ratio} \)
- Bilateral infiltrative changes on chest radiograph
- No sign of hydrostatic pulmonary oedema (pulmonary arterial occlusion pressure \( \leq 18 \text{ mm Hg or central venous pressure } \leq 15 \text{ mm Hg} \))
- No other risk factor for acute lung injury

Possible TRALI
Same as for suspected TRALI, but another risk factor present for acute lung injury

Delayed TRALI
Same as for (possible) TRALI and onset within 6–72 h of blood transfusion
## TRALI: Risk Factors

<table>
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<tr>
<th>Type of study and inclusion</th>
<th>Population</th>
<th>Country</th>
<th>Study year</th>
<th>Risk factors</th>
<th>Odds ratio (95% CI)</th>
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*Vlaar and Juffermans. Lancet 2013 Apr 30. pii: S0140-6736(12)62197-7*
TRALI: First Hit / Second Hit Hypothesis

First hit (patient factors):
- Sepsis
- Haematological malignancy
- Heart surgery
- Mechanical ventilation
- Massive blood transfusion
- Chronic alcohol abuse
- Age of patient
- Shock
- Acute renal failure
- Severe liver disease
- Spine surgery
- Liver surgery

Second hit (transfusion factors):
- RBC
  - HLA or HNA
  - Bioactive lipids
  - sCD40L
  - Aged erythrocyte
- FFP
  - HLA or HNA
- PLT
  - HLA or HNA
  - Bioactive lipids
  - sCD40L

Vlaar and Juffermans. Lancet 2013 Apr 30. pii: S0140-6736(12)62197-7
TRALI

• Caused by leukocyte antibodies in the donor (PRBCs, plasma, PLTs) that react with recipient leukocytes
  – First hit: systemic process causing neutrophil localization to pulmonary capillary endothelium
  – Second hit: blood transfusion triggers TRALI via antibody-mediated or non-antibody-mediated mechanisms
  – Leukocytes adhere to pulmonary endothelium, release proteolytic enzymes and toxic oxygen metabolites, causing pulmonary endothelial damage

• Management: supportive care, diuresis, restrictive tidal volume mechanical ventilation
TACO

• Transfusion-associated circulatory overload
• Hydrostatic pulmonary edema resulting from cardiac decompensation due to volume overload
• Signs/Symptoms: dyspnea, hypoxia, HTN, pulmonary edema on CXR
• CXR not helpful in distinguishing TRALI, TACO
• Clinical findings: LV fxn normal to decreased, increased PAOP, elevated BNP
• Management: hemodynamic monitoring, diuresis
Anaphylactic Reactions

• Caused by antibodies against IgA, complement C4, haptoglobin, other plasma proteins
• Pts who are IgA-deficient, have anti-IgA antibodies may experience an anaphylactic reaction if they receive blood products containing IgA
• Management: epinephrine IM 0.3-0.5 mg of 1 mg/mL (1:1000), adjunctive treatment with antihistamines, glucocorticoids, bronchodilators, IV fluids, other vasopressors
Reactions to Platelet Transfusions

• Caused by:
  – Cytokine accumulation in stored platelets
  – PLT antibodies
  – HLA antibodies
  – Leukocytes contained in the platelet concentrates

• Platelets may become trapped in the pulmonary capillaries

• Symptoms: chills, fever, dyspnea, pulmonary edema

• More common when stored platelets are used
Bacterial Contamination

• Second-leading cause of transfusion-related deaths (after hemolytic reactions)
• Accounts for >10% of transfusion-related deaths
• ~1/3000 cellular blood components are contaminated with bacteria (more common in platelets due to room temp storage)
• Symptoms: chills, fever beginning, during, or shortly after the transfusion; hypotension, nausea, vomiting, oliguria, shock, respiratory symptoms, bleeding (2/2 DIC)
• Types of bacteria: skin flora, gram negatives, endotoxin-producing
• Management: blood cultures/Gram stain from patient and from blood bag, immediate initiation of abx
Management of Transfusion Reactions

• Stop transfusion
• Leave needle in vein and infuse NS
• Obtain vitals
• Oxygen, CXR for pulmonary symptoms
• Brief focused physical exam: lungs, heart, skin, mucous membranes, assess for bleeding
• Blood sample: red blood cell compatibility testing, inspection of plasma for signs of hemolysis, tryptase
• Urine sample
• Definitive treatment
Initial Management

• Respiratory symptoms: epinephrine, oxygen, intubation
• Hypotension: epinephrine, crystalloid infusion
• Oliguria: mannitol for UOP 100 cc/hr
• Skin symptoms: diphenhydramine 20 mg IM/IV
Alloimmunization

- Alloimmunizations to red cell antigens occurs in 1/100
- Occurs secondary to prior transfusions, pregnancy
- Alloimmunization to PLTs can cause a poor response to PLT transfusion
- PLT refractoriness occurs in ~20% of multitransfused platelets
Graft-Versus-Host Disease

• Caused by viable lymphocytes contained in blood components
• Pts who are immunosuppressed are susceptible
• Transfused lymphocytes proliferate, causing fever, hepatic dysfunction, skin rash, diarrhea, marrow hypoplasia
• Prevented by using leukocyte-reduced blood
How to Trim Your Mustache

1. Trim your mustache weekly. First comb dry mustache with a fine toothed mustache comb. When wet, hair can appear longer, leading you to cut off too much.

2. Using mustache scissors or electric trimmer, trim first for shape, cutting along bottom of stache and then outer edges. Work from middle towards one side, then to other side and back to middle. Look straight ahead and maintain neutral face to get smooth, even line.

3. Now trim for length. Comb through stache and cut hair on outside of comb to desired length. Trim conservatively at first. If using electric trimmer, move from longer to shorter guides. You can always trim off more, but you can’t add it back after you’ve clipped it.

4. Comb through your mustache one last time, and clip any hairs you may have missed.

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TRIM

• Blood product transfusion has an immunomodulating effect
• Can be prevented with leukocyte reduced blood
• Altered graft survival in organ transplantation
  – Kidney
  – Liver
  – Bone marrow
• Increased susceptibility to malignancy recurrence
  – 60 studies with conflicting results
• Increased susceptibility to postoperative infection
  – Colorectal
  – Vascular
  – Orthopedic
Blood Transfusion for Lower Extremity Bypass Is Associated with Increased Wound Infection and Graft Thrombosis

Tze-Woei Tan, MD, Alik Farber, MD, Naomi M Hamburg, MD, Robert T Eberhardt, MD, Denis Rybin, MS, Gheorghe Doros, PhD, Jens Eldrup-Jorgensen, MD, Philip P Goodney, MD, Jack L Cronenwett, MD, Jeffrey A Kalish, MD, Vascular Study Group of New England

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A systematic review of the effect of red blood cell transfusion on mortality: evidence from large-scale observational studies published between 2006 and 2010

Sally Hopewell,¹,² Omar Omar,² Chris Hyde,³ Ly-Mee Yu,² Carolyn Doree,¹ Mike F Murphy¹

Red Cell Transfusion and Mortality

<table>
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<tr>
<th>Study Design</th>
<th>Specialty</th>
<th>Study ID</th>
<th>Hazard Ratio (HR)</th>
<th>HR effect estimate (95% CI)</th>
<th>Odds Ratio (OR)</th>
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Does Age Matter?
Effect of PRBC Age

• Alterations occur to PRBCs during aging:
  – Bacterial contamination and overgrowth
  – Reduced oxygen-carrying capacity (loss of DPG)
  – Toxic lysophospholipids released from membrane, negatively charged phospholipids exposed (procoagulant)
  – Oxidative damage
  – Alterations in erythrocyte shape
  – Potassium accumulation

• Studies have shown adverse events with transfusion of old PRBCs
  – Pneumonia
  – ALI
  – Increased length of ICU stay
  – Increased length of hospital stay
  – Increased mortality
Hypothermia

- PRBCs are stored in refrigerator at 4 degrees C
- Cold blood transfusion may cause cardiac arrhythmias
- Large volume cold blood transfusion is associated with increased mortality
- Ideal to limit transfusion rate to 5 cc/min (=administration over 1 hour)
- Massive transfusion → ideal to warm blood to body temperature prior to transfusion
Citrate Toxicity

• Citrate anticoagulant is used in the initial collection of whole blood
• Toxicity manifests as hypocalcemia with symptoms of muscle paresthesias, twitching, anxiety, hypotension, arrhythmias
• Manage with calcium supplementation
Bleeding Tendency

• PRBCs contain very few plasma components following suspension in preservative solution
• Transfusion of blood that does not contain coagulation factors leads to bleeding tendency
• This is particularly important with massive transfusion
• Requires transfusion of platelets, plasma, and cryoprecipitate to replace deficient factors
Electrolyte and Acid-Base Imbalances

- Particularly problematic with massive transfusion
- High K+ levels
- High ammonia levels
- Acidosis
- Low Ca++ levels
Recommendations for Responsible Use of Blood Products

• Restrictive transfusion policy
• Patient-tailored transfusion policy
• Order specific transfusion products for at-risk patients
Summary

• Transfusion reactions are common and deadly
• TRALI: ALI <6 hrs from transfusion, PAOP <18
• TRIM: increased risk of surgical site infection
• TACO: increased risk of volume overload
• Consistent demonstration of increased mortality in different populations, including surgical
• Older blood may be worse