Current Risks of Transfusion--What has Changed: Immunomodulation & TRALI

Neil Blumberg MD*, Susan Roseff MD# & Joanna Heal MRCP†

*Prof. of Pathology and Laboratory Medicine and Director, Transfusion Medicine, †Assoc. Prof., Medicine, University of Rochester, Rochester, NY
#Associate Professor, Pathology, MCV
# Blood Donor Testing Chronology

<table>
<thead>
<tr>
<th>Year</th>
<th>Test</th>
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<tbody>
<tr>
<td>1938</td>
<td>Syphilis</td>
</tr>
<tr>
<td>1971/2</td>
<td>Hepatitis B</td>
</tr>
<tr>
<td>1985</td>
<td>Anti-HIV</td>
</tr>
<tr>
<td>1986/7</td>
<td>ALT, anti-HBc</td>
</tr>
<tr>
<td>1989</td>
<td>Anti-HTLV I-II</td>
</tr>
<tr>
<td>1990</td>
<td>Anti-HCV</td>
</tr>
<tr>
<td>1992</td>
<td>Anti-HIV 1,2; Anti-HCV 2.0</td>
</tr>
<tr>
<td>1995</td>
<td>Syphilis – treponemal test</td>
</tr>
<tr>
<td>1996</td>
<td>HIV antigen; Anti-HCV 3.0</td>
</tr>
<tr>
<td>1999</td>
<td>NAT:HCV, HIV</td>
</tr>
<tr>
<td>2003</td>
<td>NAT:WNV</td>
</tr>
<tr>
<td>2004</td>
<td>Bacterial detection - platelets</td>
</tr>
</tbody>
</table>
Viral Pathogens

- HIV 1,2, variant strains
- Hepatitis A*, B, C… X
- HTLV I, II
- HHV: CMV, EBV
- Parvovirus B-19*

*Transmissions occur
## Viral Pathogens: Risk of Disease per Screened Unit

<table>
<thead>
<tr>
<th></th>
<th>Serology</th>
<th>Nucleic Acid Test (NAT)</th>
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<tbody>
<tr>
<td>HIV</td>
<td>1:493,000</td>
<td>1:1,900,000</td>
</tr>
<tr>
<td>HBV</td>
<td>1:205,000</td>
<td>Not yet available</td>
</tr>
<tr>
<td>HCV</td>
<td>1:103,000</td>
<td>1:1,600,000</td>
</tr>
<tr>
<td>HTLV I,II</td>
<td>1:641,000</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
What is TRALI?

- First recognized as a discrete clinical syndrome about 20 years ago. 36 cases of TRALI over 29 months at Mayo Clinic
- Sudden onset of:
  1. Acute respiratory distress
  2. Progressive hypoxia (severe)
  3. Hypotension (moderate)
  4. Fever (1-2F)
  5. Bilateral diffuse pulmonary infiltrates on Chest X-ray
  6. With no signs of CCF or fluid overload

- Indistinguishable from ALI/ARDS
- Anti-HLA (72%) or anti-Granulocyte Abs (89%) in 1 or more donors
  Popovsk MA & Moore SB  Transfusion 1985: 25; 573-577

Within 4 hours of transfusion of blood component
TRALI: Implicated Blood Products

Most frequent with

Highest volume plasma
- FFP
- Apheresis platelets
- Random Platelet Concentrates
- RBC

Also reported with:
- Granulocytes
- Cryoprecipitate
- Whole blood

Rare reports with:
- Allogeneic Bone marrow
- Peripheral blood stem cells
- IV gammaglobulin
- Directed donations
  - Child to Mother
  - Mother to child
  - Sister in law to patient

Never reported with:
- washed products or
- pooled SD plasma
TRALI: Special Clinical Features-I

- **Onset of Symptoms**
  - Dramatic & often fulminant
  - *< 6 hours of transfusion*
  - 90% occur within 1-2 hours of onset of transfusion
  - Sometimes within 5-30 mins
  - Reports of mild symptoms < 6 hours with rapid resolution and reappearance of severe symptoms at 24 hours

- **Usually due to transfusions that contain plasma**
  - Generally volume of plasma infused is ≥ 60ml
  - Can occur 10ml
TRALI: Chest X-Ray Post transfusion

Non-specific

LUNGS
Classic:
• Bilateral pulmonary infiltrates
• Interstitial & alveolar
• At time of reaction

Early:
• Patchy & mild
• May be dependant & unilat in decubitus

Late:
• White out

CXR is indistinguishable from ARDS
TRALI: A Diagnosis of Exclusion

- High Index of suspicion
- No rapid or conclusive test
- Rule out:
  1. **Cardiogenic Pulmonary edema due:**
     - Heart Disease (Left ventricular failure)
     - Fluid overload
  2. Pulmonary infection, or embolus
  3. Transfusion reactions (11% have dyspnoea)
     - Hemolytic TR, FNHTR
     - Allergic, anaphylactic
     - Bacterial contamination
  4. Other causes ARDS
1st event
A clinical condition which causes activation of pulmonary endothelium (due to release of pro-inflammatory mediators intravascularly) leading to sequestration, adhesion & priming of PMN
- Sepsis, Trauma
- Recent Surgery
- Massive transfusion
  - Cytokine administration
  - Hematological malignancies
  - Cardiac disease- Bypass surgery
  - DIC

2nd event
Transfusion of biologic response modifiers:
1. WBC antibodies (Plasma)
2. Biologically active lipids &/or cytokines released during storage of blood components (RBC & plt, but not FFP)
3. CD 40L (PLT,WB, Non-LR RBC)
4. Immune complexes
   - These activate
     - adherent primed PMN to
     - undergo respiratory burst
     - release granule content
     - causing endothelial damage, capillary leak, ALI
Treatment of TRALI - I

- Make correct diagnosis
- Prompt, vigorous & based on pathophysiology
- Increased endothelial cell permeability results in:
  - Fluid and protein leak into the alveolar spaces;
  - Pulmonary edema
  - Large fluid loss- severe hypovolemia
  - Lungs become stiff
- Stop the transfusion of blood product
- Patients with severe TRALI should be transferred to ICU
- Consider monitoring LA pressure (Swann- Ganz) to:
  - exclude cardiogenic edema
  - guide fluid management
General Approach is Supportive - II

- Supplemental Oxygen & Ventilatory support
  - Mild: supplement O₂ only and supportive care
  - Mod: Intubation, Mechanical ventilation, PEEP
    - Low tidal volume with low plateau pressures as for ARDS
- IV fluids to restore circulatory volume
  - often unresponsive to fluids, require pressor agents
- Avoid diuretics
TRALI: Clinical Outcome

• Rapid improvement: 80%
  – Often clinical improvement before CXR clears
    • Symptoms and oxygenation < 48 hours
    • clearing of infiltrates on CXR in < 96 hours
  – no permanent sequelae in survivors

• Slow resolution: 20%
  – Hypoxemia & infiltrates persists > 7 days

• Mortality 5-10% of cases cf 30-50% in ARDS
  – May occur acutely
  – During mechanical ventilation
  – Multi-organ failure
Summary

- TRALI- family of Acute Lung Injury syndromes, is the leading cause of transfusion associated deaths reported to FDA
- Under-recognized & under-reported
- Best evidence suggests a “two-hit” pathogenesis
- Complex interplay between WBCs, endothelial cells, & transfused donor antibodies, PMN-priming lipids & cytokines results in pulmonary endothelial injury & edema
- Prevention remains controversial
- Treatment is supportive with O₂, ventilation and fluids
- Recovery is expected in 90% of patients
Immunomodulation by Transfusion and Leukocyte Reduction in 2006

Three Persisting Questions

1. Are there enough indications to go to 100% leukoreduction?

2. Is the immunomodulation that follows blood transfusion clinically important and can it be abrogated by leukoreduction?

3. Is it cost effective?
Proven Benefits of Leukoreduction

- Reduced febrile transfusion reactions
- Reduced HLA alloimmunization/reduced platelet refractoriness
- Reduced CMV transmission
- Reduced post-operative infections (disputed)
- Reduced cardiac surgery mortality (disputed)
Graft Survival Versus Transfusion Dose, 1978-82, UCLA Registry

Percent Graft Survival

- 5-10 Units: n=1,436
- 1-4 Units: n=2,652
- No Transfusions: n=2,391

p < 0.001 for all curves

Months Posttransplant

3 6 12
Graft Survival in Recipients of 1-5 Units of Blood (Transplantation 35: 320, 1983)

One Year Graft Survival Rate

<table>
<thead>
<tr>
<th>Blood Component Transfused</th>
<th>Survival Rate</th>
</tr>
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<tbody>
<tr>
<td>Whole Blood</td>
<td>67</td>
</tr>
<tr>
<td>Red Cells</td>
<td>62</td>
</tr>
<tr>
<td>Washed Cells</td>
<td>51</td>
</tr>
<tr>
<td>Frozen Cells</td>
<td>41</td>
</tr>
</tbody>
</table>
Percentage of patients surviving recurrence free.
Fig. 2. The relationship between infectious complications and blood transfusion requirements.
Survival Rates of Balb/c Mice Undergoing Transfusion With Different Fractions of Blood

% of Survival*

Saline (control)  Plasma  RBCs  WBCs

Fraction of Blood Transfused

*Subjects used were undergoing burn injury and bacterial gavage at the time of transfusion.

Transfusion. 1993;33:458.
Survival Rates of Balb/c Mice Undergoing Transfusion With Three Different Doses of Allogeneic WBCs

<table>
<thead>
<tr>
<th>Dose</th>
<th>% of Survival</th>
</tr>
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<tbody>
<tr>
<td>Saline (control)</td>
<td>80</td>
</tr>
<tr>
<td>Low $6 \times 10^5$</td>
<td>60</td>
</tr>
<tr>
<td>Medium $6 \times 10^6$</td>
<td>40</td>
</tr>
<tr>
<td>High $6 \times 10^7$</td>
<td>20</td>
</tr>
</tbody>
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*Subjects used were undergoing burn injury and bacterial gavage at the time of transfusion.*

Transfusion. 1993;33:458.
- B Cell
- T Cell
- Macrophage
- IL-2; IL-12
- γ-interferon
- IL-4; IL-5; IL-6; IL-10
- Cytotoxic T Cell (DTH response)
- Antibody Formation

T helper type 1 response

T helper type 2 response
Effect of donor specific transfusions, in mice, on the production of IL-4, IL-10, and IL-2 from mitogen stimulated spleen cultures over time

Babcock and Alexander, Transplantation 61:465-468, 1996
“Good” Th1 processes antagonized by allogeneic transfusion

- Antibacterial immunity
- Antitumor immunity
- Antiviral immunity
“Bad” Th1 processes antagonized by allogeneic transfusion

- Allograft rejection
- Rejection of the fetus as an allograft
- Inflammatory diseases such as Crohn’s, Rheumatoid Arthritis, Type I Diabetes
Data from the studies of Lone Jensen, et al.
Post-Operative Infection Rate (%) or Lung Cancer Incidence/18,000 population

Smoking
Allogeneic Transfusion

Exposure Dose
0, 1-14, 15-24 and 25+ cigarettes per day [BMJ 2: 1525, 1976]
0, 1, 2, 3 units in orthopedic surgery [Transfusion 31: 212, 1991 and 32: 517, 1992]
Clinical Trials of Immunomodulation

- 7 of 9 fully published randomized trials of leukoreduction found evidence of benefit
- 4 of 6 randomized trials of autologous transfusion found evidence of benefit
- 7 of 9 implementation trials of leukoreduction found evidence of benefit
  - Thus 18 of 24 trials (75%) found evidence for abrogation of transfusion immunomodulation by leukoreduction or autologous techniques
Caveats in Interpreting Randomized Trials of Transfusion Immunomodulation

- In the European trials 70-80% leukoreduced transfusions (BC poor) are compared with 99.9% leukoreduced transfusions.

- In the autologous predonation trials 30% of patients in the autologous arm received allogeneic blood.

- In multicenter studies there was no standardization of surgical, anesthetic and postoperative management.
Misapplication of the intention to treat principle in meta-analyses of LR

- Patients randomized but not transfused should not be included in the data analysis--all meta-analyses have included such patients, as did three of the nine trials.

- Conclusions about the efficacy of LR in preventing post-operative infections cannot be drawn from data on patients receiving no transfusions.
Misapplication of the intention to treat principle in meta-analyses of LR

- The published meta-analyses arbitrarily assigned hundreds of non-transfused patients and their infections, in equal numbers, to each arm of the study.
  - These patients had been excluded by the original authors.
  - This rendered the results non-significant in some cases.

- Evidence based medicine cannot consist of adding back to the analysis patients for whom you have no data whatever.
  - Fictional data cannot be used to draw scientific conclusions.
Leukoreduced transfusions reduce by about half the odds of post-operative infection.
Limitations of the Existing Trial of ULR--Transfusion 42:1114 (2002)

- More than one in eight patients in the LR arm received some non-LR blood (12.6%)

- Patients in the LR arm were significantly more likely to receive non-LR blood than patients in the non-LR were to receive LR blood (p=0.0055)
Leukoreduction decreases post-operative mortality in cardiac surgery

- Death rate reduced from 7.8% to 3.5% (van de Watering 1998), and 10.1% to 5.5% (Bilgin 2001) in randomized trials of leukoreduced transfusions.
- Death rate reduced from 5.3% to 3.2% in our implementation trial with LR blood (p= NS).
- Post-operative infection has a mortality of 8-15% and is the leading cause of multiorgan failure syndromes.
Number to treat to save one life (NNT)

- **Nucleic Acid Testing (NAT) for HIV/HCV**
  - 500,000 to 1,000,000
    » Cost per life saved = $2.5-5,000,000

- **Leukoreduction of allogeneic transfusions in cardiac surgery**
  - 20
    » Cost per life saved = $400-600
Estimates of Cost Reduction with Leukoreduction/Autologous Transfusions in Surgery

- Jensen (Transfusion 35: 719, 1995) [Leukoreduction]
  - $2,000 decrease in costs per unit transfused
  - $1,000 to $1,500 decrease in costs per unit transfused
- Leveque (Orthoped Transactions JBJS 20: 114, 1996) [Autologous]
  - $1,100 decrease in costs per unit transfused
- Blumberg (Transfusion 40[Suppl.]: 130S, 2000) [Leukoreduction]
  - $700 decrease in costs per unit transfused

- Nationwide: 6 million units x $1,000-2,000 = $6-12 billion saved
Estimated deaths potentially averted in surgical patients by leukoreduced transfusions

- 2 million surgeries with transfusion
  - 10% fewer infections = 200,000 fewer infections
  - 8-15% of infections lead to death
  - 16,000 to 30,000 fewer deaths per year

- Cardiac Surgery: 750,000 cases per year
  - 2-4% fewer deaths
  - 15,000 to 30,000 fewer deaths per year
Top Ten Transfusion Risks 2006*

- Multi-organ failure in surgery/critical care
- Increased post-operative infection
- Increased tumor recurrence
- Increased lung injury
- Increased severity of existing infections
- Increased incidence of thrombosis
- Viral infections we don’t know about yet
- ABO mismatched transfusions
- Bacterial contamination of platelets
- Transmission of odd-ball organisms (mycoplasma, chlamydia, etc.)

*Developed world
Top Ten Transfusion Risks 2006*

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