Transfusion-related Acute Lung Injury
Presented at FDA
Blood Products Advisory Committee Meeting
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Early Synonyms for TRALI

- Leukoagglutinin Reaction
- Pulmonary hypersensitivity reaction
- Non-cardiogenic pulmonary edema
- Adult respiratory distress syndrome
- Allergic pulmonary edema
What is TRALI?

- Acute respiratory distress
- Hypoxemia (severe)
- Hypotension (moderate)
- Acute pulmonary edema
- Fever (1-2°C elevation),
- 1-2 hours of transfusion of plasma-containing blood products
### What is TRALI?

**Predominant presenting symptoms (N=46)**

<table>
<thead>
<tr>
<th>Sign/Symptoms</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory distress</td>
<td>76</td>
</tr>
<tr>
<td>Hypotension</td>
<td>15</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15</td>
</tr>
</tbody>
</table>

[Popovskyy & Haley, Immunohemotology 2000;16]
What is TRALI?
Differential Diagnosis

- Anaphylactic transfusion reaction
- Circulatory overload
- Bacterial contamination
- Cardiac failure
Who Is At Risk?

- No common thread
- Male:female ratio is about 1:1
- Patients have ranged from very young to very old
- No common underlying diagnosis
Implicated Blood Products

- Whole blood
- FFP
- RBC (all anticoagulant/preservatives)
- Granulocytes (by apheresis)
- Cryoprecipitate
- Platelet concentrate
- Plateletpheresis
- IVIG (rare)
What is the frequency of TRALI?

Incidence:

- Unknown
- Mayo Clinic Study 1:5000 plasma-containing transfusions

[Popovský & Moore, Transfusion 1985]
What is the frequency of TRALI?

Underdiagnosed:

> 240 cases published or reported

- 0.32% of severe respiratory reactions to random donor platelets (46/14,602 transfusions). [Clarke et al, Blood 1994]

- More frequent among patients with hematological disease and cardiac disease

- Average age of platelets 4.5 days
What is the frequency of TRALI?

Underdiagnosed (cont.):

Cooperman and Price, 1970:

- 40 patients with pulmonary edema in the operating setting
- 50% of cases were due to circulatory overload/unknown causes
### What is Clinical Outcome? Morbidity (N=36)

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required oxygen support</td>
<td>36</td>
<td>100%</td>
</tr>
<tr>
<td>Required mechanical ventilation</td>
<td>26</td>
<td>72%</td>
</tr>
<tr>
<td>Pulmonary infiltrates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid resolution (≤ 96 hrs)</td>
<td>29</td>
<td>81%</td>
</tr>
<tr>
<td>Slow resolution (&gt; 7 days)</td>
<td>6</td>
<td>17%</td>
</tr>
<tr>
<td>Mortality</td>
<td>2</td>
<td>6%</td>
</tr>
<tr>
<td>Long-term sequelae</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Popovskyy & Moore, Transfusion 1985;25*

*Popovskyy & Haley, 2000 (2000): 13% died*
FDA data on deaths from transfusion, 1990-1998.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>161</td>
<td>50%</td>
</tr>
<tr>
<td>#3</td>
<td>29</td>
<td>9%</td>
</tr>
</tbody>
</table>
Mortality (cont.)

SHOT 2000 Annual Report

- 18 cases
- Major morbidity: 12
- Death: 6
- 2nd most common cause of death
Pathogenesis

HLA Class I / Granulocyte Antibodies

- Precise mechanism is unknown
- Donor HLA or granulocyte-specific antibodies (anti-NB2, -NA2, -5b): 60-85% of cases
- HLA antibody/antigen correspondence: 50% of cases
- Antibodies activate complement
Pathogenesis (2)

HLA Class I / Granulocyte Antibodies

- C5a promotes neutrophil aggregation/sequestration in microvasculature of lung
- There is margination of neutrophils in pulmonary microvasculature
- Activated neutrophils release proteases, superoxide radicals: results in endothelial cell injury → pulmonary edema
Pathogenesis (3)

TRALI EX VIVO LUNG MODEL

Perfusate

5b pos PMN + Anti-5b + Complement
(human) (human) (rabbit)

Exp. Protocol

Evaluation of Lung injury

Rabbit lungs perfused for a 6 hrs
Repetitive hydrostatic challenges performed at timed intervals

Measurements of:
Pulmonary Artery Pressure
Lung weight gain

Seeger et al, Blood:76, 1990
Pathogenesis (4)
**Pathogenesis (5)**

**Implicated Antibodies**

<table>
<thead>
<tr>
<th></th>
<th>HLA</th>
<th>Granulocyte</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor</td>
<td>28%</td>
<td>41%</td>
<td>50%</td>
</tr>
<tr>
<td>Recipient</td>
<td>7%</td>
<td>4%</td>
<td>11%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>61%</td>
</tr>
</tbody>
</table>

[Popovskyy & Haley, 2000]
Role of Multiparous donor plasma

- Prospective, randomized study
- 102 ICU patients receiving ≥ 2 units FFP
- Multiparous (≥ 3 pregnancies) donors vs. controls
- 5 patients had clinical reactions → 1 TRALI
  - Donor was multiparous
- ↓ PaO₂/FiO₂ (p< 0.05) in multiparous-donor vs. control plasma

(Palfi et al, Transfusion 2001:41)
HLA Class II antibodies:
3 cases that were negative for Class I/granulocyte antibodies

(Kopko et al, 1999 & 2000)
Pathogenesis (8)

Alternative hypothesis (Silleman et al)

- May combine the antibody model with the cytokine model
- Underlying disease $\rightarrow$ endogenous cytokines
- Infusion of granulocyte/HLA antibodies or biologically active lipids
- Granulocyte activation $\rightarrow$ endothelial damage
Prevention Research

- Identify at risk recipients:
  - Prospective
  - Multicenter Studies
- Role of leukodepletion
- Educate clinicians
Regulatory Recommendations

- Quarantine untransfused components traced to implicated donors
- Defer donors previously implicated from future plateletpheresis donations
- Divert plasma-containing components from future donations (whole blood) by implicated donors → RBC/ washed RBC only
Conclusion

- TRALI is an under-diagnosed, serious problem

- Represents a spectrum of lung injury (NCPE → ARDS)