Transfusion-related Acute Lung Injury (TRALI)

Mark R. Looney, M.D.
University of California, San Francisco
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TRALI: Case presentation

- 58 year-old female with degenerative scoliosis is admitted for revision of a previous posterior spinal fusion

- Procedure: laminectomy, removal of hardware, posterior spinal fusion with hardware and bone grafts

- No significant Past Medical History
58 y/o female with scoliosis

- Intra-operative course complicated by significant blood loss

- Arterial blood gases
  - Intra-op (0900): 7.45/37/430 (1.0)
  - Intra-op (1600): 7.37/45/219 (1.0)
  - ICU arrival (1800): 7.23/73/152 (1.0/5)
<table>
<thead>
<tr>
<th>DATE</th>
<th>TIME</th>
<th>WBC</th>
<th>HCT</th>
<th>PLAT</th>
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<td>34.7</td>
<td>303</td>
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<td>7.7</td>
<td>28.6</td>
<td>137</td>
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<td>5.5</td>
<td>26.2</td>
<td>131</td>
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<td>1355</td>
<td>1.2</td>
<td>27.0</td>
<td>96</td>
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<td>1500</td>
<td>1.1</td>
<td>27.2</td>
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<td>1735</td>
<td>3.2</td>
<td>33.1</td>
<td>47</td>
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<td>2315</td>
<td>5.0</td>
<td>25.4</td>
<td>109</td>
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<td>7/3/02</td>
<td>0400</td>
<td>6.1</td>
<td>26.6</td>
<td>100</td>
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<td>7/4/02</td>
<td>0230</td>
<td>8.7</td>
<td>28.7</td>
<td>73</td>
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<tr>
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<td>0430</td>
<td>8.0</td>
<td>26.9</td>
<td>87</td>
</tr>
<tr>
<td>7/6/02</td>
<td>0415</td>
<td>7.3</td>
<td>30.8</td>
<td>119</td>
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Transfusion-related acute lung injury (TRALI)

- First cases described in 1950’s

- AKA
  - Pulmonary leukoagglutinin reaction
  - Allergic pulmonary edema
  - Pulmonary hypersensitivity reaction
  - Non-cardiogenic pulmonary edema

- TRALI coined by Popovskvsky and Moore

TRALI

- Defined as ALI/ARDS developing during or within 6 hours of a blood product transfusion

- Immunologic reaction leading directly to ALI

- Must exclude volume overload or cardiogenic pulmonary edema

- Must exclude other causes of ALI/ARDS
# TRALI - Definitions

<table>
<thead>
<tr>
<th>Canadian Consensus Conference</th>
<th>NHLBI Expert Panel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kleinman S et al.</td>
<td>Toy P et al.</td>
</tr>
<tr>
<td>Transfusion 2004</td>
<td>Crit Care Med 2005</td>
</tr>
<tr>
<td>AECC clinical definition of ALI + any blood product within 6 hours</td>
<td>AECC clinical definition of ALI + any blood product within 6 hours</td>
</tr>
<tr>
<td>TRALI: only if no other ALI risk factors</td>
<td>TRALI: can diagnose in the presence of other ALI risk fx’s</td>
</tr>
<tr>
<td>Possible TRALI: if ALI risk factors are present</td>
<td>No laboratory testing required</td>
</tr>
<tr>
<td>No laboratory testing required</td>
<td>No laboratory testing required</td>
</tr>
</tbody>
</table>
Adverse Outcomes from Transfusions

- TRALI – one of many risks
  - Hemolytic reactions, hypothermia, coagulopathy
- Association studies with mortality
- Specific organ failure – Pulmonary
  - Transfusion-related acute lung injury (TRALI)
  - Transfusion-associated circulatory overload (TACO)
  - Anaphylaxis
- Infectious risks
  - Transmission of infections (platelets)
  - Transfusion-related immunomodulation (TRIM)
Epidemiology: electronic surveillance system at UCSF and Mayo Clinic

<table>
<thead>
<tr>
<th>463,207 units</th>
<th>24 x 7 Computer surveillance for hypoxemia in recipients post-transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>47,783 patients</td>
<td></td>
</tr>
<tr>
<td>14,472 alerts</td>
<td>Alerts reviewed by Study Coordinators</td>
</tr>
<tr>
<td>561 alerts</td>
<td>Reviewed by the Expert Panel</td>
</tr>
<tr>
<td>91 patients</td>
<td>TRALI cases (only 1 case with a major ALI risk factor)</td>
</tr>
</tbody>
</table>
TRALI - Epidemiology

- Incidence:
  - 1 in 3000 blood products transfused

- Under-reported and under-recognized
  - Only 40/91 cases reported to the UCSF/Mayo blood banks

- #1 cause of mortality related to blood transfusions
Mortality Data from the U.S. FDA

Figure 1: Transfusion-Related Fatalities by Complication, FY2005 through FY2009

<table>
<thead>
<tr>
<th>Complication</th>
<th>FY05</th>
<th>FY06</th>
<th>FY07</th>
<th>FY08</th>
<th>FY09</th>
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<tbody>
<tr>
<td>TRALI</td>
<td>29</td>
<td>35</td>
<td>34</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>HTR (non-ABO)</td>
<td>16</td>
<td>9</td>
<td>2</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>HTR (ABO)</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Microbial Infection</td>
<td>8</td>
<td>7</td>
<td>6</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>TACO</td>
<td>1</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
# Clinical Outcomes from TRALI

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>Cases (n)</th>
<th>Cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen support</td>
<td>36</td>
<td>100</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>26</td>
<td>72</td>
</tr>
<tr>
<td>Pulmonary infiltrates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid resolution (&lt; 96 hrs)</td>
<td>29</td>
<td>81</td>
</tr>
<tr>
<td>Slow resolution (≥ 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>

Popovskv et al. Transfusion, 1985
Clinical Features

• Onset
  – Sudden
  – Classically, 30 – 60 min after initiation of transfusion, with a range of 0-6 hours

• Signs and symptoms
  – Fever, hypotension, tachycardia, and tachypnea
  – Hypoxemia often requiring mechanical ventilation
  – CXR: bilateral alveolar infiltrates consistent with ALI/ARDS
Chest Radiography

Immediately after transfusion

Chest CT
Diagnosis

- New ALI/ARDS within 6 hours of a plasma-containing blood product transfusion = TRALI
- Must rule out volume overload (TACO)
- Probable TRALI assigned when other ALI risk factors are present
- Role of blood bank (antibody testing) is adjunctive
Diagnostic Algorithm

- New onset hypoxemia: PaO2/FIO2 <300 or arterial oxygen saturation <90% on room air
- Chest x-ray: new or worsening bilateral infiltrates consistent with pulmonary edema
- Symptoms started within 6h of transfusion

**Alternative Diagnosis Criteria**
- Edema/plasma protein concentration >0.85*
- Pulmonary artery occlusion pressure <18 mm Hg*
- BNP < 250 or pre/post transfusion BNP ratio <1.5 OR
- The absence of rapid improvement with volume (preload) reduction** OR
- Two of the following:
  - Systolic ejection fraction >45 and no severe valvular heart disease
  - Systolic BP<160
  - Vascular Pedicle Width <65 mm and Cardio-thoracic ratio <0.55

*at the onset of acute respiratory failure
**Diuretics, positive pressure ventilation

---

Hydrostatic pulmonary edema

- New ECG ischemic changes OR
- New Troponin T >0.05

Yes

Cardiac ischemia

No

TACO

Permeability pulmonary edema

Clear temporal relationship to another ALI risk factor (sepsis, aspiration)

No

TRALI

Yes

ALI (possible TRALI)
# TACO vs. TRALI

<table>
<thead>
<tr>
<th>Feature</th>
<th>TRALI</th>
<th>TACO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body temperature</td>
<td>Fever can be present</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Hypotension</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>Acute dyspnea</td>
<td>Acute dyspnea</td>
</tr>
<tr>
<td>Neck veins</td>
<td>Unchanged</td>
<td>Can be distended</td>
</tr>
<tr>
<td>Auscultation</td>
<td>Rales</td>
<td>Rales, S3 may be present</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Diffuse, bilateral infiltrates</td>
<td>Diffuse, bilateral infiltrates</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>Normal, decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>PA occlusion pressure</td>
<td>18mmHg or less</td>
<td>Greater than 18mmHg</td>
</tr>
<tr>
<td>Pulmonary edema fluid</td>
<td>Exudate</td>
<td>Transudate</td>
</tr>
<tr>
<td>Fluid balance</td>
<td>Positive, even, negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Response to diuretic</td>
<td>Minimal</td>
<td>Significant</td>
</tr>
<tr>
<td>White count</td>
<td>Transient leukopenia</td>
<td>Unchanged</td>
</tr>
<tr>
<td>BNP</td>
<td>&lt;200 pg/ml</td>
<td>&gt;1200 pg/ml</td>
</tr>
<tr>
<td>Leukocyte antibodies</td>
<td>Donor leukocyte antibodies present,</td>
<td>Donor leukocyte antibodies may or</td>
</tr>
<tr>
<td></td>
<td>crossmatch incompatibility between don</td>
<td>may not be present; positive results can</td>
</tr>
<tr>
<td></td>
<td>donor and recipient</td>
<td>suggest TRALI even with true TACO cases</td>
</tr>
</tbody>
</table>

Challenges in the Clinical Assessment of TACO and TRALI

- Data set is often incomplete
- Determining the volume status of a patient is difficult
- Pulmonary arterial lines are being used less and less
- CXR is an insensitive test for pulmonary edema
Dynamic leukopenia in TRALI

Looney et al.  Chest 2004
Chest Radiography

Immediately after transfusion

1 day later

Pathogenesis

• TRALI has been associated with all plasma-containing products
  – High plasma volume products (FFP and platelets) are the most implicated products

• Even small amounts of plasma can trigger the reaction
  – RBCs, cryoprecipitate
TRALI Pathogenesis

• Two-event hypothesis

• First event
  – Immunologic priming by infection, surgery, mechanical ventilation, cardiopulmonary bypass, other

• Second event
  – Transfusion of any blood product, though FFP>platelets>RBCs implicated
  – Passive transfer of “biologic response modifiers (BRMs)”
    • Cognate antibody (HLA Class I/II, HNA)
    • Lipids that accumulate in stored, cellular products (lysophosphatidylcholines)
    • Other BRMs
Neutrophil Involvement in TRALI

[Graph showing percent neutrophils in lung over time with error bars and legend indicating treatment groups: isotype, Neutrophil depletion + MHC I mAb, and MHC I mAb.

[Graph showing excess lung water (µl) with error bars and legend indicating treatment groups: Neutrophil depletion + MHC I mAb, and MHC I mAb with a significance marker (**).]
Role of Platelets in TRALI

Anti-platelet Treatment with Aspirin

Treatment

- Stop the transfusion

- Rule out other causes of pulmonary edema, especially volume overload or cardiac dysfunction
  - Possibility of co-existing permeability and hydrostatic edema

- Lung protective ventilation

- Diuretics can be harmful in the hypovolemic patient

- No role for corticosteroids

- Remember that with supportive care, most patients will recover quickly
TRALI Prevention

• Multiparous females have been implicated in TRALI reactions
  – These donors have a high prevalence of HLA alloimmunization (>20% with ≥3 pregnancies)

• Fresh frozen plasma and HLA Class I and II antibodies are frequently implicated in TRALI reactions

• In 2006, AABB recommended that high plasma volume blood products (FFP, platelets) be obtained from males only or from females with no history of pregnancy
TRALI Incidence: UCSF + Mayo

Overall P=0.0008

Incidence per 10^4 units transfused

Before

After

Mitigation

Received High-Risk Unit

Did Not Receive High-Risk Unit

<0.0001

0.89

0.5

1

1.5

2

2.5

3
Plasma Mitigation and TRALI Incidence

- **UK SHOT program**
  - Decrease in TRALI incidence with male-only plasma (www.shotuk.org)

- **American Red Cross**
  - Decrease in TRALI incidence with male-predominant plasma (Eder AF et al. Transfusion 2010)

- **Netherlands**
  - 33% reduction in TRALI cases with male-only plasma (Wiersum-Osselton JC et al. Transfusion 2010.)
Conclusions

• TRALI is the #1 cause of mortality from blood transfusions in many countries

• Many countries are reporting a decrease in TRALI incidence with plasma mitigation

• TRALI is a clinical diagnosis that can be made at the bedside

• ALI/ARDS + blood transfused within 6 hours = TRALI