Transfusion-related Acute Lung Injury (TRALI): Pathophysiology and Prevention

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Sociedad Chilena de Hematologia

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Objectives

1. Review a clinical case of TRALI
2. Discuss the pathophysiology of TRALI
3. Describe the current strategies taken by blood donor centers to reduce the risk of TRALI
Case: Presentation

- 18-year-old male with T cell lymphoblastic lymphoma
- In the pediatric intensive care unit for 10 days recovering from bacterial (Gram-negative rod) sepsis
- Vital signs stable, no respiratory distress before transfusion
- Receives 1 apheresis platelet unit for low platelet count (12 x 10^9/L)
Case: Transfusion reaction

- One hour after receiving the apheresis platelet unit (450 mL; 3rd day of storage), reported chest tightness, dyspnea
- Acute respiratory distress
- Hypoxemic, O₂ sats <70s
- Intubated, noted to have copious pink frothy secretions from airway; Blood gas FiO₂ 100%; O₂ 48.7; sat 68.9
Case: Chest X-ray

Transfusion-related acute lung injury (TRALI)

Before Transfusion

20’ After
Case: Clinical Course

• Supportive treatment
  – Mechanical ventilation, low tidal volume
  – Diuretics not indicated, may be harmful

• Chest X-ray: Showed improvement of pulmonary edema within 24 hrs

• Blood center investigation revealed serologic evidence of TRALI
  – HLA Class II match between female multiparous platelet donor (anti-DR4) and patient (DR4⁺)
# Canadian Consensus Definition

<table>
<thead>
<tr>
<th>Condition</th>
<th>Criteria</th>
<th>Marked</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute onset</strong></td>
<td>(within 6 hours of transfusion)</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Hypoxemia</strong></td>
<td>(SpO₂ &lt; 90% on room air)</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Bilateral infiltrates on frontal CXR</strong></td>
<td>Evidence of pulmonary edema</td>
<td>✓</td>
</tr>
<tr>
<td><strong>No evidence of circulatory overload</strong></td>
<td>Pulmonary artery pressure &lt; 18 mm Hg</td>
<td>✓</td>
</tr>
<tr>
<td><strong>No preexisting ALI before transfusion</strong></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td><strong>No other risk factor for acute lung injury</strong></td>
<td>(e.g., sepsis, aspiration, pneumonia, cardiopulmonary bypass)</td>
<td>✓</td>
</tr>
</tbody>
</table>

*(if present, Possible TRALI)*

Kleinman S, *et al* Transfusion 44, 1774 2004
TRALI vs. TACO

- 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

- Edema/plasma protein concentration >0.65*
- Pulmonary artery occlusion pressure <18 mm Hg*
- BNP < 250 or pre/post transfusion BNP ratio <1.5
- The absence of rapid improvement with volume (preload) reduction**
- 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)

Yes

ALI (possible TRALI)

No

TRALI

TRALI: Pathogenesis

Noncardiogenic pulmonary edema

TRALI Etiology:

- Direct Granulocyte activation by HLA or HNA antibodies
- Neutrophil activation by underlying disease with triggering by transfused bioresponse modifiers

Ware and Matthay, NEJM 353:2788, 2005.
### Anti-leukocyte Antibodies

<table>
<thead>
<tr>
<th>Anti-Granulocyte antibodies</th>
<th>HLA Class I antibodies</th>
<th>HLA Class II antibodies</th>
</tr>
</thead>
</table>

#### “Two-hit” Hypothesis

- Biologically active lipids
- Cell membrane fragments
- LPS – lysophosphatidyl choline

<table>
<thead>
<tr>
<th>Direct binding to neutrophils and monocytes</th>
<th>Underlying condition results in priming of neutrophils</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binding to endothelium - Indirect activation of neutrophils through Fc receptors</td>
<td>Biologic response mediators (e.g., lipids) activate primed neutrophils</td>
</tr>
</tbody>
</table>

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**Neutrophil activation**
TRALI: Pathogenesis

TRALI in Single Lung Transplant

Antibody binding to pulmonary endothelium

<table>
<thead>
<tr>
<th></th>
<th>HLA type</th>
<th>Anti-HLAAb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>A1,3</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>B35,62</td>
<td></td>
</tr>
<tr>
<td>Lung donor</td>
<td>A2,3</td>
<td>Not tested</td>
</tr>
<tr>
<td></td>
<td>B14, 44</td>
<td></td>
</tr>
<tr>
<td>Blood donor</td>
<td>A2,3</td>
<td>Anti-B44</td>
</tr>
<tr>
<td></td>
<td>B7,8</td>
<td></td>
</tr>
</tbody>
</table>
Prevalence of HLA Abs in donors

- Background rate of HLA antibody in presumably non-immunized donors is similar for men and women (1-4%)
- Transfusion history in men has a minimal effect on HLA antibody prevalence (3.4% vs. 4% for untransfused vs. transfused)
- HLA antibody prevalence increases with the number of pregnancies (<1%, never pregnant; 10.4%, 1 pregnancy; 31.1% >3 pregnancies)

# Recipient tracing studies

## Prior recipients of blood from implicated donors

<table>
<thead>
<tr>
<th>Study</th>
<th>Antibody</th>
<th>Recipients</th>
<th>Rxns (TRALI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kopko 2002</td>
<td>HNA-3a</td>
<td>36</td>
<td>15 (2)</td>
</tr>
<tr>
<td>Win, 2002</td>
<td>Multiple</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Cooling, 2002</td>
<td>HLA-I</td>
<td>20</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Fadeyi, 2007</td>
<td>HNA-2a</td>
<td>32</td>
<td>12 (0)</td>
</tr>
<tr>
<td>Nicolle, 2004</td>
<td>HLA-I,II</td>
<td>18</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Toy, 2004</td>
<td>HLA-I,II</td>
<td>103</td>
<td>4 (0)</td>
</tr>
<tr>
<td>Zupanska, ‘07</td>
<td>HLA-I,II</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>259</strong></td>
<td><strong>35 (5)</strong></td>
</tr>
</tbody>
</table>
U.S. Reported TRALI Fatalities

FDA, Fiscal Years

2003-2005 2006

AABB Bulletin

www.FDA.GOV; Holness L et al, TMR 18:3;184-8
2001-2002:
  FFP was involved in 60% of TRALI cases
Oct 2003:
  Switch to predominantly male plasma
After 2004:
  Sustained reductions in TRALI with plasma for transfusion and platelet pooling from male donors

Recommendations to reduce the incidence of TRALI:

1. Implement interventions to minimize the preparation of high plasma-volume components from donors known to be leukocyte-alloimmunized or at increased risk.
2. Work towards implementing appropriate evidence-based hemotherapy practices in order to minimize unnecessary transfusion.
3. Monitor the incidence of reported TRALI and TRALI-related mortality.

For all high plasma-volume components:

1. Complete full implementation of the measures relating to plasma components and whole blood by November 2007.
2. Complete full implementation of the measures relating to platelet components no later than November 2008.
U.S. Reported TRALI Fatalities

FDA, Fiscal Years

- 2003-2005
- 2006-2008
- 2009

AABB Bulletin

Number of cases

BPAC 2004

FDA Alert; BPAC 2001

www.FDA.GOV; Holness L et al, TMR 18:3;184-8
Distributions (Denominators):

- 6 M Packed Red Cell Units
- 1.7 M Plasma Products
- 850,000 Apheresis Platelets
- 250,000 Random Donor Platelets
- 40,000 Pooled Platelets
**TRALI Investigation**

### Probability Codes

<table>
<thead>
<tr>
<th>Probability Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>P6 (HIGH)</td>
<td>Consistent with TRALI/Possible TRALI, donor source identified/donor implicated</td>
</tr>
<tr>
<td>P5 (HIGH)</td>
<td>Consistent with TRALI/Possible TRALI, donor source not confirmed</td>
</tr>
<tr>
<td>P4 (HIGH)</td>
<td>TRALI/Possible TRALI cannot be excluded</td>
</tr>
<tr>
<td>P3 (LOW)</td>
<td>TRALI/Possible TRALI unlikely, other cause more likely</td>
</tr>
<tr>
<td>P2 (LOW)</td>
<td>TRALI/Possible TRALI not supported</td>
</tr>
<tr>
<td>P1 (LOW)</td>
<td>Case rescinded</td>
</tr>
</tbody>
</table>

Eder et al. ARC Hemovigilance Program
TRALI Investigation

All cases ARC regions, 2003-9

2003-2005
2006-2008
2009

Year

Number of Cases

2003 2004 2005 2006 2007 2008 2009

2006-8: Eder et al. Transfusion, 2010; 50:1732-1742
2009: ARC Hemovigilance Program
Probable TRALI by Component

Fatalities reported to ARC, 2003 to 2005

38 Fatalities
“Probable TRALI”

No Antibody detected
Female donor with Antibody

Eder et al. Transfusion. 2007; 47:599-607
Transfusion-related Acute Lung Injury

• **Plasma components** were responsible for most TRALI cases reported to the American Red Cross Hemovigilance Program between 2003-2005

• Most TRALI cases and associated fatalities were linked to **female, HLA or HNA antibody-positive donors**

• “Prudent measures to limit transfusion of HLA/HNA antibody-containing plasma components may prevent as many as **6 fatalities per year** …”

Plasma from Male Donors

Calendar Years 2006-8

• In 2006, the American Red Cross began preferentially distributing plasma collected from male donors for transfusion in an effort to reduce the risk of TRALI.

• Evaluate the effect of the male-predominant plasma strategy on the rate of reported TRALI cases and associated fatalities.
Plasma from Male Donors

Calendar Years 2006-8

Plasma from Male Donors (%)

Goal

95%

Implementation

Eder et al. Transfusion, 2010; 50:1732-1742
Plasma from Male Donors

By Labeled ABO Type, CY2009

Total distributed: 1,673,099

Plasma Units for Transfusion (%)

<table>
<thead>
<tr>
<th>Blood Type</th>
<th>Female Donors</th>
<th>Male Donors</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>0.8</td>
<td>99.2</td>
</tr>
<tr>
<td>A</td>
<td>0.9</td>
<td>99.1</td>
</tr>
<tr>
<td>B</td>
<td>3.2</td>
<td>96.8</td>
</tr>
<tr>
<td>AB</td>
<td>40.1</td>
<td>59.9</td>
</tr>
</tbody>
</table>

ARC Hemovigilance Program, CY2009
Probable TRALI

Reported fatalities, 2006-9

2006-8: Eder et al. Transfusion, 2010; 50:1732-1742
2009: ARC Hemovigilance Program

* p value 0.01
** p value, 0.02 vs. 2006
Probable TRALI

Nonfatal cases, 2006-9

Number of Cases

<table>
<thead>
<tr>
<th>Year</th>
<th>Plasma</th>
<th>RBC</th>
<th>Aph Plt</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Single Component Type Investigated

OR 95% CI, vs 2006

* 0.26 (0.10-0.57)

** 0.34 (0.16-0.72)

2006-8: Eder et al. Transfusion, 2010; 50:1732-1742

2009: ARC Hemovigilance Program
### Reported TRALI, CY2009

#### Plasma transfusion

<table>
<thead>
<tr>
<th>Plasma</th>
<th>RBC</th>
<th>Gender</th>
<th>ABO</th>
<th>Plasma Antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (1)</td>
<td>(1)</td>
<td>F (M,F)</td>
<td>AB+</td>
<td>A9,25,32; Bw4,Cw2,5,6,15,18; and HNA-3a(5b)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>F</td>
<td>B+</td>
<td>Multiple Class I and Class II (DQ6; DR15)</td>
</tr>
<tr>
<td>1(1)</td>
<td></td>
<td>F, (M)</td>
<td>AB+</td>
<td>Multiple Class I (A3) and Class II specific</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>F</td>
<td>AB+</td>
<td>A2,9,28;B8,17;DR7,9;DQ2,4,9</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>F</td>
<td>AB-</td>
<td>Class II positive</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>F</td>
<td>AB+</td>
<td>Multiple Class I and II (both donors)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>F,M</td>
<td>AB+</td>
<td>Not tested</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>F,M</td>
<td>AB+</td>
<td>Not tested</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>M</td>
<td></td>
<td>HNA-1a; HNA-1b</td>
</tr>
<tr>
<td>1 (1)</td>
<td></td>
<td>F (M)</td>
<td>AB+</td>
<td>Negative</td>
</tr>
</tbody>
</table>

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No fatalities reported from plasma transfusion

ARC Hemovigilance Program
Conclusion: TRALI from plasma transfusion was significantly reduced in 2009 vs. 2006 (10 vs 32 cases; OR 95% CI 0.31 (0.15-0.62)

ARC Hemovigilance Program
Conclusions

• Male-predominant plasma strategy effectively reduced the risk of TRALI in the American Red Cross

• Residual risk associated with plasma in 2008-9 (1 in ~200,000 distributed plasma units) is from female antibody-positive donors
  – aim is to reach 100% plasma from male donors
  – challenge is to meet demand for group AB plasma

• Strategies for apheresis platelets are being implemented
• Questions?

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