TACO vs. TRALI: Recognition, Differentiation, and Investigation of Pulmonary Transfusion Reactions

Shealynn Harris, M.D.
Assistant Medical Director
American Red Cross Blood Services
Southern Region
Case Presentation

• 74 year-old female with GI bleed
• Transfused
  – 1 unit Apheresis Platelets
  – 4 units RBCs
• During transfusion
  – Difficulty breathing
  – Hypoxia
  – Increased respiratory rate
Considerations: Transfusion Reaction

• Pulmonary Transfusion Reaction
  – Transfusion-associated circulatory overload (TACO)
  – Transfusion-related acute lung injury (TRALI)

• Transfusion Reaction with Pulmonary Symptoms
  – Allergic (anaphylaxis)
  – Septic Transfusion Reaction
Other Considerations

- Myocardial infarction
- Acute respiratory distress syndrome (ARDS)
- Sepsis
- Drug reaction
- Pneumonia
Challenges in Characterizing Pulmonary Symptoms Associated with Transfusion

- Recognizing a transfusion reaction
- Differentiating between possible etiologies
  - Criteria for diagnosis
  - Diagnostic tools
- Contributing factors (e.g., underlying disease)
- Obtaining complete clinical and laboratory information
- Investigating donors and understanding results of investigation
Case Presentation

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- Transfused
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  - Hypoxia
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Pre-Transfusion

Transfusion-Associated Pulmonary Edema: TACO vs TRALI
Pulmonary Edema

Abnormal accumulation of fluid in the lung
Pulmonary Edema

• Cardiogenic (hydrostatic)
  – TACO
  – Myocardial Infarction

• Non-cardiogenic (permeability)
  – TRALI
  – ARDS
Transfusion-Associated Circulatory Overload (TACO)

- Volume overload temporally associated with transfusion

- **Signs and Symptoms**
  - Shortness of breath
  - Increased respiratory rate
  - Hypoxemia
  - Increased left atrial pressure
  - Jugular venous distension
  - Elevated systolic blood pressure
Transfusion-Associated Circulatory Overload (TACO)

• **Incidence**
  - Overall: 0.1% - 1%
  - Elderly: up to 8%
  - Critical Care: 2% - 11%

• **Mortality**
  - Estimated 5 - 15%
Transfusion-Associated Circulatory Overload (TACO)

• **Treatment**
  – Oxygen
  – Possible intubation and mechanical ventilation
  – Diuresis to reduce volume

• **Also consider Myocardial Infarction**
Transfusion-Related Acute Lung Injury (TRALI)

- Leakage of fluid into alveolar space due to diffuse alveolar capillary damage

- **Signs and Symptoms**
  - Shortness of breath
  - Increased respiratory rate
  - Hypoxemia
  - Hypotension
  - Occasionally fever
Transfusion-Related Acute Lung Injury (TRALI)

• **Incidence**
  – Overall: 0.16% per patient
  – Critical Care: 0.08% per unit transfused
  – Tertiary Care: 0.04% per unit transfused

• **Mortality**
  – Estimated 5% - 10%
Transfusion-Related Acute Lung Injury (TRALI)

• Treatment
  – Oxygen
  – Possible intubation and mechanical ventilation
  – Possible fluids to treat hypotension

• Also consider ARDS
Transfusion-Related Acute Lung Injury (TRALI)

NHLBI Definition

“TRALI is defined as new acute lung injury occurring during or within 6 hrs after a transfusion, with a clear temporal relationship to the transfusion….”

Transfusion-Related Acute Lung Injury (TRALI)

Canadian TRALI Consensus Conference Definition

- **TRALI**
  - New occurrence of acute onset acute lung injury (with hypoxemia and bilateral infiltrates on chest x-ray but no evidence of left atrial hypertension
  - Not preexisting BUT
  - Emerging during or within 6 hours of the end of transfusion AND
  - Having no temporal relationship to an alternative acute lung injury risk factor
Transfusion-Related Acute Lung Injury (TRALI)

Canadian TRALI Consensus Conference Definition

• Possible TRALI
  – Cases in which there was a temporal association with an alternative risk factor
TRALI is a Diagnosis of Exclusion

We must rule out all other possible etiologies before rendering a diagnosis of TRALI
TACO vs. TRALI
Diagnostic Tools: Chest X-ray

- **Pros:**
  - Identify pulmonary edema
  - Identify pleural effusions (more consistent with TACO)
  - See evidence of other pulmonary disease
- **Cons:**
  - Does not show specific mechanism of edema
  - Radiology reports are often vague
- **Suggested to measure vascular pedicle width and cardiothoracic ratio to improve specificity (never seen this)**
TACO vs. TRALI
Diagnostic Tools: Pulmonary Artery Occlusion Pressure

- Insertion of catheter into pulmonary artery to measure back pressure from heart

- Pros
  - Definitive measurement

- Cons
  - Invasive
  - Increased morbidity and mortality
  - Interobserver variability
  - Lacks sensitivity and specificity

www.emedicine.com
TACO vs. TRALI
Diagnostic Tools: Pulmonary Edema Fluid Protein Concentration

• Small catheter inserted into the alveoli to measure lung fluid protein concentration
• Blood sample to measure plasma protein concentration
• Calculate ratio pulmonary edema/plasma protein concentration

• Pros:
  – Sensitive measurement

• Cons:
  – Mostly used in research
  – Not very feasible in clinical setting
  – Must sample as soon as patient is intubated (difficult timing)
TACO vs. TRALI
Diagnostic Tools: Echocardiography

• Sound waves used to measure heart function

• Pros
  – Not invasive
  – Sensitive and specific for measuring left heart function (ejection fraction)

• Cons
  – Normal test DOES NOT rule out cardiogenic pulmonary edema
TACO vs. TRALI

B-type Natriuretic Peptide (BNP)

- Hormone released from heart with volume expansion in ventricles from pressure overload
- BNP <250 pg/mL more consistent with TRALI

Pros:
- Easy to measure
- Sensitive and specific indicator of cardiogenic pulmonary symptoms
- Pre-transfusion to post-transfusion ratio has relatively good sens and spec
- Can be used to rule out TACO

Cons:
- Biological variability
- Who measures BNP before transfusion?
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 mmHg

BNP < 250 or pre/post transfusion BNP ratio < 1.5

Absence of rapid improvement with volume reduction (diuretics)

Two of the following:

- Systolic ejection fraction >45 and no sever valvular heart disease
- Systolic BP <160
- Vascular Pedicle Width <65 mm and Cardio-thoracic ratio <0.55

CARDIOGENIC PULMONARY EDEMA

NON-CARDIOGENIC PULMONARY EDEMA
CARDIOGENIC PULMONARY EDEMA

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

YES → Cardiac Ischemia

NO → TACO

NON-CARDIOGENIC PULMONARY EDEMA

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

NO → TRALI

YES → Possible TRALI

<table>
<thead>
<tr>
<th><strong>TRALI</strong></th>
<th><strong>TACO</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dyspnea</strong></td>
<td>YES</td>
</tr>
<tr>
<td><strong>Arterial blood gas</strong></td>
<td>Hypoxemia</td>
</tr>
<tr>
<td><strong>Blood Pressure</strong></td>
<td>Low to Normal</td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
<td>Normal to Elevated</td>
</tr>
<tr>
<td><strong>BNP</strong></td>
<td>Low (&lt;250 pg/mL)</td>
</tr>
<tr>
<td><strong>Pulm artery occlusion pressure</strong></td>
<td>Low to Normal</td>
</tr>
<tr>
<td><strong>Echocardiogram</strong></td>
<td>Normal heart function</td>
</tr>
<tr>
<td><strong>Response to Diuretics</strong></td>
<td>Worsens</td>
</tr>
<tr>
<td><strong>Response to Fluids</strong></td>
<td>Improves</td>
</tr>
</tbody>
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What about Testing for Donor Leukocyte Antibodies?

Anti-HLA
Anti-Granulocyte (anti-HNA)
TRALI and Leukocyte Antibodies

• Pathogenesis of TRALI is not clear
• Few controlled experimental studies of TRALI
• Lack of in vivo animal model
• Two Hypotheses
  – Donor leukocyte antibodies bind to recipient neutrophils which cause acute lung injury
  – Bioactive lipids in stored blood “prime” neutrophils which cause acute lung injury
<table>
<thead>
<tr>
<th>Test</th>
<th>n</th>
<th>%</th>
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<tr>
<td>Granulocyte antibodies</td>
<td></td>
<td></td>
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<tr>
<td>Patient</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Donor</td>
<td>32</td>
<td>89</td>
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<tr>
<td>Lymphocytotoxic antibodies (donor)</td>
<td>26</td>
<td>72</td>
</tr>
<tr>
<td>HLA-specific antibodies</td>
<td>11*</td>
<td>65</td>
</tr>
<tr>
<td>HLA-antigen (patient)/antibody correspondence</td>
<td>10*</td>
<td>59</td>
</tr>
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<table>
<thead>
<tr>
<th>Pregnancies</th>
<th>Number Tested</th>
<th>Number Sensitized</th>
<th>Percentage of Women Sensitized</th>
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<tbody>
<tr>
<td>0</td>
<td>103</td>
<td>8</td>
<td>7.8</td>
</tr>
<tr>
<td>1</td>
<td>33</td>
<td>5</td>
<td>15.2</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>10</td>
<td>14.3</td>
</tr>
<tr>
<td>3</td>
<td>58</td>
<td>15</td>
<td>25.9</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>10</td>
<td>30.3</td>
</tr>
<tr>
<td>&gt;5</td>
<td>27</td>
<td>6</td>
<td>22.2</td>
</tr>
<tr>
<td>All women</td>
<td>324</td>
<td>54</td>
<td>16.6</td>
</tr>
</tbody>
</table>
UK SHOT Data

- TRALI risk is 5 to 7 fold greater in components containing high volume of plasma
- Majority of TRALI cases involved leukocyte-antibody positive female donors
- Oct 2003: UK moved to male-only plasma
- Significant reduction in TRALI cases in UK since Jan. 2004

www.shot-uk.org
ARC Data

• TRALI reports 2003-2005 (n = 550)
• 38 cases of probable TRALI
  – 24 related to plasma transfusion
  – 75% cases involved plasma from leukocyte-antibody positive female donors

Eder A et al. Transfusion 2007 in press.
TRALI: In Vivo Mouse Model


<table>
<thead>
<tr>
<th>Components (n)</th>
<th>Class I n (%)</th>
<th>Class II n (%)</th>
<th>Class I &amp; Class II n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBCs (106)</td>
<td>7 (7)</td>
<td>8 (8)</td>
<td>3 (3)</td>
<td>18 (17)</td>
</tr>
<tr>
<td>Cryo (66)</td>
<td>3 (5)</td>
<td>3 (5)</td>
<td>10 (15)</td>
<td>16 (24)</td>
</tr>
<tr>
<td>Plts (59)</td>
<td>7 (12)</td>
<td>5 (9)</td>
<td>1 (2)</td>
<td>13 (22)</td>
</tr>
<tr>
<td>FFP (77)</td>
<td>9 (12)</td>
<td>4 (5)</td>
<td>9 (12)</td>
<td>22 (29)</td>
</tr>
<tr>
<td>All Components (308)</td>
<td>26 (8)</td>
<td>20 (7)</td>
<td>23 (8)</td>
<td>69 (22)</td>
</tr>
</tbody>
</table>
Challenges

• No clear test for TRALI
• Leukocyte antibody positive donor DOES NOT equal TRALI diagnosis
• Incidence of HLA antibodies in donors is very high relative to number of TRALI cases
• Many TRALI cases are not associated with leukocyte antibodies
• Massive transfusion: odds are high that at least one donor will be positive
Case Presentation

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  - Increased respiratory rate
Investigation of Pulmonary Transfusion Reactions

• Rule out EVERYTHING before diagnosing TRALI
• Clinical Presentation: Need as much information as possible
• Timeline of Events: Temporal relationship of transfusion to symptoms
• Diagnostic Studies: Chest x-ray, BNP, Echocardiogram, Blood cultures
• Donor Testing: only if highly suspicious for TRALI
  – Male donor: no testing unless transfusion hx
  – Female donor: if test positive, then defer
  – HLA crossmatch positive: more supportive of TRALI
Summary

• Several etiologies to consider with pulmonary symptoms during transfusion
• Pulmonary edema within 6 hrs of transfusion consider TACO and TRALI
• Consider clinical presentation and all diagnostic studies
• No specific diagnostic study
• TRALI is a DIAGNOSIS OF EXCLUSION
• TRALI is not diagnosed by positive leukocyte antibody test alone