Pulmonary Consequences of Transfusion

The Bill Teague Lecture
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Haemonetics Corporation
Agenda

- Overview of transfusion-associated pulmonary complications
- TACO
- TRALI
- Research agenda
Eras of Transfusion Medicine

1900 1975 2000 Present
Era Red Cell Compatibility Infectious Disease TRALI & Other Complications
Component Therapy

- Hypotensive reactions
- Acute Pain Reactions
- “WBIT”
Differential Diagnosis of Transfusion Associated - Respiratory Distress

- Circulatory Overload (TACO)
- TRALI
- Allergic/Anaphylactic transfusion reaction
- Bacterial contamination
- Acute hemolytic reaction
- Not transfusion related
Transfusion-Associated Circulatory Overload (TACO)

Definition/Mechanism

- Pulmonary edema due to transfusion
  - Too much blood +/- non-sanguineous fluid
  - Transfused too rapidly
- Cardiogenic
- Role of cytokines?
### TACO: Clinical Profile

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Very young/old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>&lt; 2 hours of transfusion</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Respiratory distress, cyanosis, headache, dry cough</td>
</tr>
<tr>
<td>Signs</td>
<td>↑ BP; systolic &gt; diastolic; ↑ HR; ↑ CVP; ↑ wedge pressure</td>
</tr>
<tr>
<td>Laboratory</td>
<td>↑ B- natriuretic peptide</td>
</tr>
</tbody>
</table>
Demographics of TACO

- Quebec Hemovigilance System: 2000-2006

<table>
<thead>
<tr>
<th>Age Distribution</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-17</td>
<td>2.6%</td>
</tr>
<tr>
<td>18-49</td>
<td>6.9%</td>
</tr>
<tr>
<td>50-59</td>
<td>7.3%</td>
</tr>
<tr>
<td>60-69</td>
<td>19.3%</td>
</tr>
<tr>
<td>70+</td>
<td>64%</td>
</tr>
</tbody>
</table>

Robillard et al. Transfusion 2008;48:204A
## Incidence of TACO

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Year</th>
<th>Population</th>
<th>Incidence/Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Popovskv</td>
<td>1996</td>
<td>THA/TKA</td>
<td>0.01</td>
</tr>
<tr>
<td>Bierbaum</td>
<td>1999</td>
<td>THA/TKA</td>
<td>0.08</td>
</tr>
<tr>
<td>Finlay</td>
<td>2005</td>
<td>General</td>
<td>0.01</td>
</tr>
<tr>
<td>Robillard</td>
<td>2008</td>
<td>General</td>
<td>0.03</td>
</tr>
</tbody>
</table>

21% Life-threatening
TRALI & TACO: Critically Ill Patients

**Mayo Study**

- Consecutive patients @ 4 ICUs
- NOT requiring respiratory support at time of transfusion
- Nested case-control design
- 8902 units transfused in 1351 patients

*R. Rana et al. Transfusion 2006;46:1478-1483*
TRALI / TACO in Critically Ill Patients

<table>
<thead>
<tr>
<th></th>
<th>TRALI Suspected</th>
<th>TRALI Possible</th>
<th>TACO</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>7</td>
<td>17</td>
<td>25</td>
<td>1:1271</td>
</tr>
<tr>
<td>Incidence</td>
<td>1:1271</td>
<td>1:534</td>
<td>1:356</td>
<td></td>
</tr>
</tbody>
</table>

*R. Rana et al. Transfusion 2006;46:1478-1483*
TRALI vs. TACO

- 80% of suspected cases of “TRALI” were diagnosed as TACO (Mayo Clinic)

- UCSF Study
  - Prospective screening of post-transfusion hypoxemia
    - 88 cases “flagged” by computer system
      - 4 TRALI
      - 6 TRALI/TACO
      - 10 TACO alone

- TRALI & TACO are frequently confused

Importance of TACO: FDA Mortality Data

<table>
<thead>
<tr>
<th></th>
<th>% of Fatalities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FY05</td>
</tr>
<tr>
<td>TRALI</td>
<td>47%</td>
</tr>
<tr>
<td>TACO</td>
<td>2%</td>
</tr>
</tbody>
</table>
TACO: Diagnosis
Role of B-natriuretic peptide

- Neurohormone released from ventricular myocardium in response to ventricular volume & pressure distension
- First introduced to diagnose CHF
- Zhou et al: Post/pre-transfusion ratio of 1.5, sensitivity of 81% & specificity of 89% to diagnose TACO
- Tobian et al: Comparable findings

References:
- Zhou et al. Transfusion 2005;45:1056-63
- Tobian et al. Transfusion 2007;47:7A
Transfusion Flow Rate: RBC

- Requirements
  - Circular of Information (USA): As patient can tolerate, but less than 4 hours
  - AABB Technical Manual: Recommends 2-4 ml/min
Flow Rate: RBC (cont.)

- **Problem**
  - No accounting of recipient weight (blood volume)
  - No physiologic basis for current recommendations
Flow Rate: RBC (cont.)

- **Problem:**
  - 2005 study (USA): 47 cases of TACO
    - Mean: 4.5 ml/min.
    - Range: 0.9 – 48.1 ml/min.
  - TACO occurs with flow rates as low as 0.9 ml/min.

- **Implications:**
  - Recipient weight should be factored
  - Need better quality control of infusion process and pumps
  - Need data for better nursing guidelines

Popovský MA. Transfusion Reactions, 2007
TACO: Prevention

- Evidence-based component therapy
- RBC transfusion by the gram of hemoglobin
  - Arslan et al. Transfusion 2004;44:485-88
    - Matched Hgb requirements with blood bank units
- Standardized RBC dosing
  - Automation +/- 3% variability
  - Manual units: 30-40% variability
TACO: Possible Role of BRM

- IL-6 & TNF-2 may play a role in CHF
- Do BRM play a role in TACO?
- Does leukoreduction decrease TACO?
- Single center, observational, retrospective

<table>
<thead>
<tr>
<th>Period</th>
<th>% LR</th>
<th>TACO/100,000 Components</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989-1999</td>
<td>&lt;100%</td>
<td>6.6</td>
<td>P=0.03</td>
</tr>
<tr>
<td>2000-2007</td>
<td>100%</td>
<td>3.3</td>
<td></td>
</tr>
</tbody>
</table>

Blumberg et al. Transfusion 2008;48:202-203A
TACO: Summary

- TACO is an important clinical diagnosis
  - Significant morbidity
  - Increased recognition of mortality
- It is a frequent complication of transfusion
- It is under-recognized and under-diagnosed
- Confused with TRALI
TRALI: The First Definition

- Acute respiratory distress
- Hypoxemia: PaO₂ of 30-50 torr
- Bilateral pulmonary edema: rapid onset
- Hypotension: moderate
- Fever (1-2°C)
- Within 6 hours of a plasma-containing transfusion
- Exclusions: Underlying cardiac failure/respiratory disease

Early Synonyms for TRALI

- Allergic pulmonary edema
- Non-cardiogenic pulmonary edema
- Pulmonary leukoagglutinin reaction
- Pulmonary hypersensitivity reaction
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, Immunohematology 2000;16]
Clinical Features

- **Timeline:** Symptoms from onset of transfusion
  - >90% of cases within 1-2 hours
  - 100% of cases within 6 hours
- **Plasma-containing transfusions**

Popovsky MA & Moore SB. *Transfusion 1985;25:573-577*
TRALI: Most Frequently Implicated Blood Products

- Red Blood Cells
- Fresh Frozen Plasma
- Apheresis platelets
- Platelet concentrates
## Clinical Course

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>N</th>
<th>%</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;25:573-577*
FDA: Transfusion-Associated TRALI Deaths

<table>
<thead>
<tr>
<th>Year</th>
<th>% of All Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>30.9%</td>
</tr>
<tr>
<td>2005</td>
<td>36.6%</td>
</tr>
<tr>
<td>2006</td>
<td>56%</td>
</tr>
<tr>
<td>2007</td>
<td>65%</td>
</tr>
<tr>
<td>2008</td>
<td>35%</td>
</tr>
</tbody>
</table>
## TRALI Incidence

<table>
<thead>
<tr>
<th>Period</th>
<th>Investigation</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1982-1985</td>
<td>Popovskyy</td>
<td>1:5000</td>
</tr>
<tr>
<td>Late 1990’s</td>
<td>Wallis</td>
<td>1:7900</td>
</tr>
<tr>
<td>2000-2005</td>
<td>Silliman</td>
<td>1:1300</td>
</tr>
</tbody>
</table>
Mortality in the USA

- Reported death rate: 5-24%; most frequent cited rate is 5-10%
- Assumptions
  - Incidence: 1:5000
  - Plasma-containing transfusions: 20,000,000 per year
  - Number of cases: 4000 per year
  - Number of fatal cases: 200-400 (5-10% mortality)
TRALI is Under-reported

- Retrospective chart review of 50 patients receiving blood from a donor linked to fatal TRALI

Kopko et al. JAMA 2002;287:1968
TRALI is Under-reported (cont.)

- 36 chart reviews included
- 7 mild/moderate reactions (16.7%)
- 8 severe reactions (22.2%)
- 2 had 2 reactions
- Only 2 of 8 severe reactions reported to transfusion service

Kopko et al. JAMA 2002;287:1968
TRALI Incidence: By Blood Product

Product: FFP > Whole Blood ≥ Apheresis >> RBC Platelet Pools Platelets

Plasma Volume (ml): 200-300 200-300 300 40-60
TRALI Incidence-Critical Care Setting

- Mayo Clinic, consecutive patients in ICU who did not require respiratory support at time of transfusion

- **TRALI** 1:534 per unit transfused

- **TACO:** 1:356 per unit transfused

R Rana et al. Transfusion 2006;46:1478-1483
2004 Consensus Panel Criteria for TRALI

- **Acute lung injury**
  - Acute onset
  - Hypoxemia
    - $\text{PaO}_2/\text{FiO}_2 \leq 300$ or $\text{SPO}_2 < 90\%$ on room air or other clinical evidence of hypoxemia
  - Bilateral infiltrates on frontal CXR
  - No evidence of left atrial hypertension (e.g. circulatory overload)
  - No preexisting ALI before transfusion
  - During or within 6 hours of transfusion
  - No temporal relationship to an alternative risk factor for ALI

*Transfusion 2004;44:1774-1789*
2004 Consensus Panel: Possible TRALI

- Same as “TRALI” but with other risk factors for ALI
  - No preexisting ALI before transfusion
  - Risk Factors
    - Sepsis
    - Pneumonia
    - DIC
    - Drug overdose
    - Burns
    - Massive transfusion
    - Near drowning
    - Aspiration
Mild TRALI

- Chills (with/without rigors), dyspnea, modest temperature increase (<1ºC)
- Cyanosis, tachycardia
- Hypertension
- Mild oxygen desaturation
- Acute leukopenia
- Majority of cases?

*Transfusion 2007;47:105A
Transfusion 2007;47:545-550*
## Laboratory Findings

### 1980’s Mayo Clinic Studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983 (N = 5)</td>
<td>• Donor Class I</td>
</tr>
<tr>
<td></td>
<td>• HLA antibodies in 4/5</td>
</tr>
<tr>
<td></td>
<td>• Leukoagglutinating Antibodies in 5/5</td>
</tr>
<tr>
<td></td>
<td>• Antibody/Antigen correspondence in 3/5</td>
</tr>
<tr>
<td>1985 (N = 36)</td>
<td>• Donor Class I</td>
</tr>
<tr>
<td></td>
<td>• HLA/leukoagglutinating in 89%</td>
</tr>
<tr>
<td></td>
<td>• Aby/Ag correspondence in 59%</td>
</tr>
<tr>
<td></td>
<td>• Recipient antibody in 6%</td>
</tr>
</tbody>
</table>
Leukopenia

Looney et al. Chest 2004;126:249-258
TRALI: Pathogenesis

Pulmonary Edema

Increased Microvascular Permeability

Leukocyte Antibodies

2-"event" model
TRALI: Who is at risk?

- Recent surgery
- Induction chemotherapy
- Cardiopulmonary bypass
- Massive transfusion
- TTP
- No differences in gender, age

TRALI: What are the Triggers?

Donor Antibodies
- HLA-I: Multiparous donors
- HLA-II: Multiparous donors
- Anti-granulocyte
  - HNA-3a
- Anti-Monocyte

Biologically Active Mediators
- Lysophosphatidylcholines (Lyso-PC’s)
- Neutral Lipids
TRALI: Antibody Hypothesis

Transfusion

HLA I, II Anti-PMN Ab’s

Activation

Intravascular

Extravascular

Airspace

EC Damage

$O_2^-$

Capillary leak

Kopko et al. Transfusion 2003
Pathogenesis (2)

TRALI EX VIVO LUNG MODEL

- **Perfusate**
  - 5b pos PMN (human)
  - Anti-5b (human)
  - Complement (rabbit)

- **Exp. Protocol**
  - Rabbit lungs perfused for 6 hrs
  - Repetitive hydrostatic challenges performed at timed intervals

- **Evaluation of Lung injury**
  - Measurements of:
    - Pulmonary Artery Pressure
    - Lung weight gain

Seeger et al, Blood:76, 1990
Pathogenesis (3)
Frequent HNA/HLA Antibodies

- HNA – 1a
- HNA – 1b
- HNA – 2a
- HNA – 3a: Severe presentation
- HLA – A2

Bux J. BrJ Haem 1996;93:707-713
TRALI: 2 Event Hypothesis

1st Hit
Surgery, Active Infection, Transfusion

LPS/ Lipids, Cytokines

2nd Hit
Transfusion

Neutral Lipids, Lyso-PC’s

Attraction Tethering adhesion Activation

Intravascular

Extravascular

Airspace

Silliman, et al. 2003
Pathogenesis: Neutrophil Priming

Ex vivo model

- Rats treated with lipopolysaccharide (LPS) or saline control before lungs isolated and perfused
- Perfusion with supernatant of 42-day stored RBC in the LPS treated rats resulted in ↑ pulmonary artery pressure/lung edema
- Saline-treated animals → no changes

_Silliman et al. Transfusion 2003;43:633-40_
Pathogenesis of TRALI

Bux & Sachs, 2008. TRALI
TRALI: Pathogenesis

Priming & activation of neutrophils

- Strong surgical association (31 of 36 cases – Popovský & Moore)
- Surgery & active infections induce neutrophil priming (Bass et al, 1986)
- Acute infection, cardiovascular disease & leukemia identified as TRALI risk factors
- Primed neutrophils adhere, retained & activated
- Once activated, release microbicidal arsenal → damage & capillary leak

TRALI: Pathogenesis

Priming & Activating Substances in Transfusions

- 61-89% of cases demonstrate leukocyte antibodies (Popovskyy 1985 & Popovskyy & Haley 2001)
- Leukocyte antibodies (e.g., anti-HLA – A2) induce neutrophil aggregation
- Priming & activation of neutrophil mechanism unclear
- Indirect activation by HLA Class II antibodies (Kopko, Transfusion 2003) of monocytes is possible
Pathogenesis

Role of Multiparous donor plasma

- Prospective, randomized study
- 102 ICU patients receiving $\geq 2$ units FFP
- Multiparous ($\geq 3$ pregnancies) donors vs. controls
- 5 patients had clinical reactions $\rightarrow 1$ TRALI
  - Donor was multiparous
- $\downarrow \text{PaO}_2/\text{FiO}_2 (p < 0.05)$ in multiparous-donor vs. control plasma

*(Palfi et al, Transfusion 2001:41)*
## Impact of Male Donor Plasma: NBS (UK)

<table>
<thead>
<tr>
<th></th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>33</td>
<td>36</td>
<td>23</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td>Deaths</td>
<td>7</td>
<td>7</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Vox Sang; 2005: P-501

\[\downarrow = \text{Policy change}\]
TRALI Deaths in USA

Source: FDA CBER, 2009
TRALI Prevention: Near Term

- Defer implicated blood donors
  - Permanent deferral
  - Washed or frozen-deglyc RBC
- Plasma from female donors should not be used for transfusion (FFP)
- Screen multiparous donors for HLA → divert from WB, FFP or apheresis platelets, if positive
- Evidence-based use of blood components, particularly FFP
Research Agenda

- Prospective, randomized studies
- What are the “early warning” indicators for TACO?
- Who is at high risk for TRALI?
- Are there other mechanisms of TRALI?
TRALI: Summary

- TRALI is an important diagnosis
- Frequently confused with TACO
- Under-diagnosed, under-reported
- Represents a spectrum of lung injury (NCPE → ARDS): Reversible