TRALI, TACO & The Struggle for Breath
2010 SHOT Conference
Manchester, U.K.

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&
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Haemonetics Corporation
Agenda

- Historical perspective
- Overview of transfusion-associated pulmonary complications
- TRALI vs. TACO
- TRALI
  - Incidence
  - Mechanism
  - Clinical Management
  - Diagnosis
  - Interventions
  - Managing the donor base
Eras of Transfusion Medicine

1900
- Red Cell Compatibility
- Blood Storage and Supply
- Component Therapy

1975
- Infectious Disease
- Apheresis
- HLA & Transplantation

2000
- Blood Supply & Safety
- Cellular Therapy
- Blood Management

Present
- TRALI & Other Complications
Differential Diagnosis of Transfusion Associated - Respiratory Distress

- Allergic/Anaphylactic transfusion reactions
- Bacterial contamination
- Acute hemolytic reaction
- Not transfusion related
- Circulatory Overload (TACO)
- TRALI
Onset: Symptoms/Signs

- TRALI
- TACO
- Anaphylactic
- Bacterial Cont
- AHTR

0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6

Hours
TACO
Transfusion-Associated Circulatory Overload
Transfusion-Associated Circulatory Overload (TACO)

Definition/Mechanism

- Hydrostatic pulmonary edema due to transfusion
  - Too much blood +/- non-sanguineous fluid
  - Transfused too rapidly
TACO

1:50 AM  9:15AM  12:05 AM

Acknowledgement: M. Looney
# TACO: Clinical Profile (textbook)

<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</td>
</tr>
<tr>
<td>Signs</td>
<td>↑BP; systolic &gt; diastolic; Tachycardia</td>
</tr>
</tbody>
</table>
TACO: Diagnosis

- Clinical: Gallop, jugular venous distension, systolic/diastolic hypertension
- Radiographic: CT ratio >0.53 & vascular pedicle width >65 mm
- EKG: New ST segment and T wave changes
- Laboratory: ↑ troponin T >0.1 ng/ml
- Hemodynamic: PAOP >18mm Hg, CVP >12
- Prompt response to appropriate therapy: Inotropic agents, diuretics

## 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>Investigator</th>
<th>Year</th>
<th>Population</th>
<th>Incidence/Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Popovsky</td>
<td>1996</td>
<td>THA/TKA</td>
<td>1%</td>
</tr>
<tr>
<td>Bierbaum</td>
<td>1999</td>
<td>THA/TKA</td>
<td>8%</td>
</tr>
</tbody>
</table>
TRALI vs. TACO

- UCSF
  - Screening of post-transfusion hypoxemia [820 patients]
    - 88 cases “flagged” by computer system as candidates for TRALI
      - 7 TRALI
      - 6 TRALI or TACO (Indeterminate)
      - 10 TACO (11%)
    - But only 2 reported!

Clinical Impact of TACO

- Increases morbidity
  - 21% of cases life-threatening (Robillard)
- Increases ICU stay (Li, 2009)
- Increases hospital length of stay (Popovskyy 1996) in orthopedic surgery
- 1 RBC is sufficient to trigger the reaction! (Popovskyy 1985 & 1996, Robillard 2008)
  - 20 – 53% of cases
## Importance of TACO: FDA Mortality Data

<table>
<thead>
<tr>
<th></th>
<th>FY05</th>
<th>FY06</th>
<th>FY07</th>
<th>FY09</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRALI</td>
<td>47%</td>
<td>56%</td>
<td>65%</td>
<td>30%</td>
</tr>
<tr>
<td>TACO</td>
<td>2%</td>
<td>13%</td>
<td>10%</td>
<td>27%</td>
</tr>
</tbody>
</table>
TACO

Quebec Hemovigilance System

<table>
<thead>
<tr>
<th>Age</th>
<th># RBC/Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-17</td>
<td>1.20</td>
</tr>
<tr>
<td>18-49</td>
<td>3.24</td>
</tr>
<tr>
<td>60-69</td>
<td>2.23</td>
</tr>
<tr>
<td>70+</td>
<td>1.84</td>
</tr>
<tr>
<td>Mean</td>
<td>2.11 ± 2.01</td>
</tr>
</tbody>
</table>

P. Robillard (personal communication)
TACO: Diagnosis
Role of B-natriuretic peptide

- Neurohormone released from ventricular myocardium in response to ventricular volume changes & 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

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

Requirements/Recommendations

- Circular of Information (USA): “As patient can tolerate, but in less than 4 hours”

  - 150 – 300 ml/hr (adults)
  - 2.5 – 5 ml/min
Flow Rate: RBC

- Problem
  - No accounting of recipient weight (blood volume)
  - No accounting of the patient’s underlying cardiac reserve
Flow Rate: RBC (cont.)

- Problem: Flow rate is poorly controlled
  - 2005 study: 47 cases of TACO
    - Mean: 4.5 ml/min.
    - Range: 0.9 – 48.1 ml/min.

- Implications:
  - TACO occurs with low flow rates as low as 0.9 ml/min.
  - Need better quality control of infusion process
  - Need data for better nursing transfusion guidelines

Andrzejewski C. (personal communication)
Popovskv MA. Transfusion Reactions, 2007
TACO: Prevention

- Evidence-based hemotherapy
- Standardized RBC dosing
  - Problem: Manual units have +/-30% variability in Hgb content & volume
  - Transfusion by the gram based on desired target hemoglobin (Arslan, 2004)

Q: Role of automated collections [Standardizes the content (+/- 7%)]?
TACO: Summary

- TACO is an important clinical diagnosis associated with significant morbidity
- It is the “new” complication of importance
- It is under-recognized and under-reported
- Confused with TRALI
- Research into “early warning” bedside indicators is warranted
TRALI
Transfusion-related acute lung injury
TRALI: The First Definition

- Acute respiratory distress
- Hypoxemia: $\text{PaO}_2$ of 30-50 torr
- Bilateral pulmonary edema: rapid onset
- Hypotension: moderate; unresponsive to fluids
- Fever (1-2°C)
- Occurs within 6 hours of a plasma-containing transfusion

Recognizing TRALI at Bedside & Surgery

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]
Classic TRALI: CXR

Immediately after transfusion

1 day later

Looney et al. Chest 2004;126:249
### TRALI: Which Components?

<table>
<thead>
<tr>
<th>Component</th>
<th>Plasma Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh Frozen Plasma</td>
<td>200 - 250 ml</td>
</tr>
<tr>
<td>Apheresis platelets</td>
<td>300 – 350 ml</td>
</tr>
<tr>
<td>Red Blood Cells</td>
<td>20 – 60 ml</td>
</tr>
<tr>
<td>Platelet concentrates</td>
<td>20 – 60 ml</td>
</tr>
</tbody>
</table>
## 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>

*Popovksy & Moore, Transfusion 1985;25:573-577*
# ARDS vs. TRALI

<table>
<thead>
<tr>
<th>Clinical:</th>
<th>ARDS</th>
<th>TRALI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Factors:</td>
<td>Septicemia, Aspiration, Multiple transfusions, DIC, Drug overdose, Fracture of long bones, Toxic inhalation</td>
<td>Infection, Inflammation, Multiple transfusions, End-stage liver disease</td>
</tr>
<tr>
<td>Morbidity</td>
<td>100% ventilation</td>
<td>80-100% ventilation</td>
</tr>
<tr>
<td>Mortality</td>
<td><strong>30-40%</strong></td>
<td><strong>5-20%</strong></td>
</tr>
<tr>
<td>Long-term injury:</td>
<td>Yes</td>
<td>No?</td>
</tr>
</tbody>
</table>
“Mild” TRALI

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

Transfusion 2007;47:105A
Transfusion 2007;47:545-550
Long-Term Survival in TRALI

Mayo Clinic

- Nested case-control (74 TRALI; 74 control)
- Evaluated in-hospital, 1 & 2 year mortality

<table>
<thead>
<tr>
<th></th>
<th>Hospital</th>
<th>1 Year</th>
<th>2 Years</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRALI</td>
<td>43</td>
<td><strong>63</strong></td>
<td><strong>74</strong></td>
<td>0.02 – 0.03</td>
</tr>
<tr>
<td>Controls</td>
<td>24</td>
<td>46</td>
<td>54</td>
<td></td>
</tr>
</tbody>
</table>

*G Li et al. Chest (in press)*
Spectrum of Acute Lung Injury

MILD          SEVERE
NCPE  TACO  TRALI  ARDS
## TRALI Deaths in USA

![Chart showing TRALI deaths in USA](chart.png)

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

Source: U.S. FDA, CBER, 2009
## TRALI: Transfusion-Associated 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>

*Source: U.S. FDA, CBER 2009*
TRALI: Incidence

<table>
<thead>
<tr>
<th>Period</th>
<th>Investigators</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>
<tr>
<td>2004</td>
<td>Finlay</td>
<td>1:1000</td>
</tr>
</tbody>
</table>

1997 – 2003 NBS (SHOT)

- RBC: 1:520,000
- FFP/Cryo: 1:58,000
- Platelets: 1:75,000
Why the Disparities in Incidence?

- Lack of common definition of TRALI
- Passive surveillance versus active case recognition systems
- Clinical versus serological confirmation
- Laboratory confirmation differs
- Underrecognition
2004 Consensus Panel Criteria for TRALI

acular Lung Injury (ALI)

- 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*
TRALI is Under-Reported

- “Lookback” study of patients receiving blood from a donor linked to fatal TRALI
- Transfusions were within 2 years of the index case
- FFP was only component collected
- Donor
  - 54 y.o. O+ g3p2
  - Strong positive anti-HNA-3A

Kopko et al. JAMA 2002;287:1968
TRALI: Underreported & Under-Recognized

TRALI “Mary”

FFP → 36 Patients

- Mild/Moderate (17%)
- Severe (22%)
- 2 Repeat Reactions
- 2 reported to transfusion service!

P Kopko et al. JAMA 2002;287:1968-71
TRALI in Medical ICU

- 225 patients: median age 58
- Multivariate analysis of risk factors of ALI
- Results
  - End-stage liver disease was strongest independent risk factor for TRALI (OR 22.4; <p .005)
  - FFP: Significant risk factor (OR 13.6; <p .001)
- Risk of ALI in liver disease

<table>
<thead>
<tr>
<th>Transfusion</th>
<th>No Transfusion</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>34.7%</td>
<td>1.3%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*A Benson (personal correspondence, 2009)*
TRALI in Critically Ill

Dutch Study

- Cohort analysis
- 114 cases of TRALI in 2235 patients

0.9% Incidence/Unit transfused
2.2% Incidence/Patient
1 case reported to Dutch surveillance!

Factors for a Complete Work-up

- Strength of diagnosis
- Involvement of high plasma volume component
- Onset of reaction timeline
# Laboratory Investigation

<table>
<thead>
<tr>
<th>Clinical Diagnosis</th>
<th>HLA * Antibody</th>
<th>HNA * Antibody</th>
<th>Patient HLA</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRALI</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Possible TRALI</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

* = Components within 2 hours of transfusion
Pathogenesis: Hypotheses

Pulmonary Edema

Increased Microvascular Permeability

Leukocyte Antibodies (Antibody-mediated)

Other mediators

2-event model

Priming

Activation
TRALI – Treatment & Management

- Stop the transfusion for early signs/symptoms
- Respiratory Support
  - As intensive as dictated by clinical picture
  - Oxygen supplementation
  - Mechanical ventilation for severe hypoxemia
- Pressure agents for sustained hypotension
- No role for corticosteroids
Interventions to Reduce Incidence of TRALI

- Increased physician/nursing education
- Segregation of plasma-rich blood components
- Donor screening through medical history
- Donor testing
TRALI Intervention Strategy

Female Donor

Plateletpheresis
- Medical History
- 1-3 Pregnancies
  - HLA Testing
    - +
    - -
  - Collection:
    - Use products
    - Retest periodically

Whole Blood
- FFP
- Fractionation
Impact of Gender-specific Plasma Transfusions on Severe TRALI
### FFP & TRALI Risk in the U.K.

<table>
<thead>
<tr>
<th>Year Range</th>
<th>Gender</th>
<th>Cases/Per Unit Distributed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999 – 2004</td>
<td>Mixed</td>
<td>15.5/million</td>
</tr>
<tr>
<td>2005 – 2006</td>
<td>Male-only</td>
<td>3.2/million</td>
</tr>
</tbody>
</table>

(P = 0.008)

C. Chapman et al. Transfusion 2009;49:440
TRALI cases 1996-2008 (SHOT)
## TRALI as Percent of Transfusion Deaths: FDA Reports

<table>
<thead>
<tr>
<th>Year</th>
<th>All (%)</th>
<th>FFP-related (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>47</td>
<td>NA</td>
</tr>
<tr>
<td>2006</td>
<td>56</td>
<td>63</td>
</tr>
<tr>
<td>2007</td>
<td>65</td>
<td>35</td>
</tr>
<tr>
<td>2008</td>
<td>35</td>
<td>25</td>
</tr>
</tbody>
</table>
TRALI Fatalities Reported to FDA
Residual Plasma: How much is too much?

NBS (U.K.)

- RBC (additive) – 2 cases
  - HLA Class I/II aby in each
  - Matched cognate Ag

- Pooled Buffy Coat Platelets (male plasma)
  - HLA Class I/II aby (1 donor)
  - Matched cognate Ag

.: 20 - 40 ml of antibody-positive plasma is sufficient to trigger a reaction!

*Transfusion Medicine 2008;18:276-280*
## Managing the Donor Base – A Schema

<table>
<thead>
<tr>
<th>Situation</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implicated</td>
<td>Permanent deferral or washed or frozen RBC</td>
</tr>
<tr>
<td>HNA antibodies but not implicated</td>
<td>Permanent deferral</td>
</tr>
<tr>
<td>HLA antibodies but not implicated</td>
<td>Low plasma blood components</td>
</tr>
<tr>
<td>Associated but not implicated</td>
<td>Flag in computer system 2\textsuperscript{nd} case → permanent deferral</td>
</tr>
</tbody>
</table>
Summary

- Pulmonary complications - TRALI & TACO - are the most serious transfusion complications today.
- TACO can be prevented with better fluid management.
- TRALI and TACO are underrecognized & underreported.
- Pathogenesis of TRALI is more clearly understood but not completely.
- Diverting female plasma has saved lives.