Transfusion Related Respiratory Complications: An Update on TRALI, TACO and TAD

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Disclosure

I have no real or apparent conflict of interest or other relationships related to the content of this presentation. There is no off-label and/or investigational use of products discussed in this presentation. I have no relevant financial relationship to disclose.
Objectives

- Provide guidance on recognition, evaluation and classification of transfusion associated respiratory complications
- Review pathophysiology of pulmonary edema including cardiogenic versus non-cardiogenic
- Present criteria for TRALI, TACO and TAD as defined by the National Healthcare Safety Network (NHSN) and ISBT/IHN/AABB
- Identify predisposing risk factors for these events
- Identify clinical and laboratory variables helpful in distinguishing respiratory complications
Hydrostatic Changes with Transfusion

Gupta SP, et al. Angiology 1982; 33:343-8

Transfusion Associated Respiratory Complications

TACO

TRALI

TAD
Incidence of severe respiratory adverse reactions per 100,000 units

- 13 countries reporting
- 2009 to 2012
- >92,000 reactions

349 Deaths with 58% related to Respiratory Complications
- TACO 26%
- TRALI 19%
- TAD 12%
Transfusion Related Fatalities
U.S. Data

Table 3: Transfusion-Associated Fatalities by Complication, FY2012 – FY2016

<table>
<thead>
<tr>
<th>Complication</th>
<th>FY12 No.</th>
<th>FY12 %</th>
<th>FY13 No.</th>
<th>FY13 %</th>
<th>FY14 No.</th>
<th>FY14 %</th>
<th>FY15 No.</th>
<th>FY15 %</th>
<th>FY16 No.</th>
<th>FY16 %</th>
<th>Total No.</th>
<th>Total %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylaxis</td>
<td>2</td>
<td>5%</td>
<td></td>
<td>0%</td>
<td>2</td>
<td>7%</td>
<td>2</td>
<td>5%</td>
<td>5</td>
<td>12%</td>
<td>11</td>
<td>6%</td>
</tr>
<tr>
<td>Contamination</td>
<td>3</td>
<td>8%</td>
<td></td>
<td>13%</td>
<td>1</td>
<td>3%</td>
<td>5</td>
<td>14%</td>
<td>5</td>
<td>12%</td>
<td>19</td>
<td>10%</td>
</tr>
<tr>
<td>HTR (ABO)</td>
<td>3</td>
<td>8%</td>
<td>1</td>
<td>3%</td>
<td>4</td>
<td>13%</td>
<td>2</td>
<td>5%</td>
<td>4</td>
<td>9%</td>
<td>14</td>
<td>8%</td>
</tr>
<tr>
<td>HTR (non-ABO)</td>
<td>5</td>
<td>13%</td>
<td>5</td>
<td>13%</td>
<td>4</td>
<td>13%</td>
<td>4</td>
<td>11%</td>
<td>1</td>
<td>2%</td>
<td>19</td>
<td>10%</td>
</tr>
<tr>
<td>Hypotensive Reaction</td>
<td>-</td>
<td>0%</td>
<td>-</td>
<td>0%</td>
<td>1</td>
<td>3%</td>
<td>1</td>
<td>3%</td>
<td>1</td>
<td>2%</td>
<td>3</td>
<td>2%</td>
</tr>
<tr>
<td>TACO</td>
<td>8</td>
<td>21%</td>
<td>13</td>
<td>34%</td>
<td>5</td>
<td>17%</td>
<td>11</td>
<td>30%</td>
<td>19</td>
<td>44%</td>
<td>56</td>
<td>30%</td>
</tr>
<tr>
<td>TRALI*</td>
<td>17</td>
<td>45%</td>
<td>14</td>
<td>37%</td>
<td>13</td>
<td>43%</td>
<td>12</td>
<td>32%</td>
<td>8</td>
<td>19%</td>
<td>64</td>
<td>34%</td>
</tr>
</tbody>
</table>

Note: FY2015-FY2016 only includes cases with an imputability of Definite/Certain, Probable/Likely, or Possible.
FY2012-FY2014 only include cases classified as transfusion-related.
*FY2012-FY2016 numbers combine both TRALI and Possible TRALI cases

# Transfusion Related Fatalities

## U.S. Data - TRALI

### TABLE 1. Major recommendations from AABB regarding TRALI risk reduction

<table>
<thead>
<tr>
<th>Year</th>
<th>Communication</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>Association Bulletin 01-04</td>
<td>Urged federally funded research on TRALI</td>
</tr>
<tr>
<td>2004</td>
<td>23rd edition of the Standards</td>
<td>Policy for testing, evaluation, and reporting of suspected TRALI cases</td>
</tr>
<tr>
<td>2004</td>
<td>Statement to the Blood Product Advisory Committee, FDA</td>
<td>Endorsed Consensus Conference definition of TRALI</td>
</tr>
<tr>
<td>2005</td>
<td>Association Bulletins 05-06 and 05-09 and the 23rd edition of the Standards</td>
<td>Definition of associated and implicated donors; management of implicated donors; laboratory evaluation of suspected TRALI cases</td>
</tr>
<tr>
<td>2006</td>
<td>Association Bulletin 06-07</td>
<td>Intervention to provide low-risk blood products; promote evidence-based hemotherapy, monitor incidence of TRALI</td>
</tr>
<tr>
<td>2007</td>
<td>Association Bulletin 07-03</td>
<td>Clarified weighing benefits of TRALI risk reduction vs. apheresis PLT availability</td>
</tr>
</tbody>
</table>

### Chart

[Graph showing number of TRALI cases from FY02 to FY16]
Is it TACO, or Is it TRALI?
Cardiopulmonary Circulation

- Shortness of breath
- Increased respirations
- Decreased oxygen saturation

Pulmonary Artery

Pulmonary veins

Superior and Inferior Vena Cava

Passive backward transmission of left-sided filling pressures

LEFT HEART

Loss of LA compliance
(exercise increased)
Mitrail regurgitation
Systolic/diastolic LV dysfunction

RV failure
Gas Exchange in Lung

[Diagram of gas exchange in the lung with labeled parts such as alveoli, capillaries, and bronchioles.]
Gas Exchange in Lung
Fluid Exchange in Lung

- Fluid moves from vascular to interstitial space based upon intra-capillary pressure (flow) and oncotic pressure of interstitial liquid.

- Opposing forces are interstitial liquid pressure and oncotic pressure of the plasma.

Ware LB, Matthay MA. N Engl J Med 353(26):2788-2796
Fluid Exchange in Lung

**Cardiogenic**
- Hydrostatic pressure increases rate of transvascular fluid filtration
- When interstitial pressure exceeds pleural pressure fluid moves into alveolar space
- Filtered edema fluid typically has low protein content

**Noncardiogenic**
- Microvascular membrane is injured
- Permeability increases allowing fluid and protein to leave the vascular space
- Alveolar spaces fill depending upon extent of interstitial edema

Ware LB, Matthay MA. N Engl J Med 353(26):2788-2796
Pulmonary Edema

Cardiogenic –

- Most commonly due to left ventricular systolic or diastolic dysfunction
  - With or without additional cardiac pathology, i.e. coronary artery disease or valve abnormalities.
- Primary fluid overload (eg, due to blood transfusion)
- Severe hypertension
- Renal artery stenosis
- Severe renal disease

Noncardiogenic -

- Acute respiratory distress syndrome (ARDS)
  - Sepsis
  - Aspiration pneumonia
  - Trauma, burn
  - Pancreatitis
  - Smoke inhalation
  - Shock
  - Stem cell transplant
  - Drug toxicity
- Neurogenic pulmonary edema
- High altitude
TACO

Comparison of Hemovigilance Definitions
Pulmonary Edema

US National Healthcare Safety Network

- In 2010, launched the hemovigilance protocol pilot to collect data on transfusion associated events within the United States.

The International Hemovigilance Network

- In Europe, a working group of the International society of Blood transfusion was formed in 2009.

Formed to provide a forum for benchmarking of data and best practice sharing, both groups have developed criteria for use in assessing and assigning a category to transfusion related adverse events.
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 6 hours: Need 3 or more</td>
<td>Occurring within 6 hrs of Tx (any 4 of following)</td>
<td>During or up to 12h after Tx (3 or more in total)</td>
</tr>
<tr>
<td>Acute respiratory distress (dyspnea, orthopnea, cough)</td>
<td>Acute respiratory distress</td>
<td>Acute or worsening (desaturation, dyspnea or cyanosis) respiratory compromise</td>
</tr>
<tr>
<td>Evidence of left heart failure</td>
<td></td>
<td>Evidence of acute or worsening pulmonary compromise:</td>
</tr>
<tr>
<td>Radiographic evidence of pulmonary edema</td>
<td>Acute or worsening pulmonary edema on frontal chest radiograph</td>
<td>- Radiographic chest imaging and/or other non-invasive assessment of cardiac function</td>
</tr>
<tr>
<td>Elevated central venous pressure (CVP)</td>
<td>Tachycardia, Increased blood pressure</td>
<td>Evidence for cardiovascular system changes not explained by the patient's underlying medical condition, including development of tachycardia, hypertension, jugular venous distension, enlarged cardiac silhouette and/or peripheral edema</td>
</tr>
<tr>
<td>Evidence of positive fluid balance</td>
<td>Evidence of positive fluid balance</td>
<td>Evidence of fluid overload including: positive fluid balance; clinical improvement with diuresis</td>
</tr>
<tr>
<td>Elevated brain natriuretic peptide (BNP)</td>
<td>Comment: an elevated BNP is supportive of TACO</td>
<td>Elevation in B type natriuretic peptide (NP) levels (e.e., BNP or NT-pro BNP) to greater than 1.5 times pretransfusion value</td>
</tr>
</tbody>
</table>

Pulmonary Edema

(a) Chest radiograph of a case of cardiogenic pulmonary edema showing cardiomegaly (black arrow) with fluffy air-space opacities in central as well as peripheral lungs.

(b) Chest radiograph of a case of noncardiogenic pulmonary edema showing batwing opacities (arrowheads) with air bronchogram and absence of cardiomegaly.

## Pulmonary Edema

<table>
<thead>
<tr>
<th>Radiographic finding</th>
<th>Cardiogenic Edema</th>
<th>Noncardiogenic Edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart size</td>
<td>Normal to enlarged</td>
<td>Usually normal</td>
</tr>
<tr>
<td>Width of vasculature</td>
<td>Normal to widened</td>
<td>Usually normal or narrowed</td>
</tr>
<tr>
<td>Distribution of edema</td>
<td>Even or central</td>
<td>Patchy or peripheral</td>
</tr>
<tr>
<td>Pleural effusions</td>
<td>Present</td>
<td>Not usually present</td>
</tr>
<tr>
<td>Peribronchial cuffing</td>
<td>Present</td>
<td>Not usually present</td>
</tr>
<tr>
<td>Septal lines</td>
<td>Present</td>
<td>Not usually present</td>
</tr>
<tr>
<td>Air bronchograms</td>
<td>Not usually present</td>
<td>Usually present</td>
</tr>
</tbody>
</table>
Central venous pressure (CVP)

Considered a measure of blood pressure in right atrium and vena cava

Pulmonary Capillary Wedge Pressure (PCWP)

Indirectly measures left atrial pressure

Catheter tip looks “through” the pulmonary circulation to “see” the left atrial pressure.
BNP

- BNP – Brain natriuretic peptide is hormone released primarily from the heart
- BNP is released by ventricular myocytes during wall stress
- Released in response to stretch of muscle fiber
- Elevated levels can be indicative of heart failure
• Literature review of 481 articles mentioning TACO
• 20 articles discuss diagnostic markers for TACO
• 7 studies have investigated biomarkers for TACO
  - Serum biomarker of fluid overload; pulmonary edema fluid protein; biomarker of inflammation; cardiac biomarkers

• Conclusions:
  - BNP and NT-proBNP test take about an hour
  - Post event NP dependable if within first 24 hrs, best at time of symptoms
  - Can measure pre-event from residual samples, NT-proBNP preferred due to stability
  - NP should not be used in critically ill population
  - Low level likely excludes TACO (BNP <300 pg/mL or NT-proBNP <2000 pg/mL)
  - Ratio ≥ 1.5 can aid in diagnosis of TACO. Lower ratio does not rule out
TACO Risk Factors

* Retrospective review of 1140 mixed ICU patients with transfusion (5.8% TACO)
  - History of heart failure
  - Renal failure
  - Degree of positive fluid balance

> Two-year prospective study of 901 transfusions in the ICU (6% TACO)
  - Transfusion volume
  - Rate of administration
  - Positive fluid balance
  - LV dysfunction was a predictor

A post hoc analysis of a case-control study of pulmonary transfusion reactions
  - Age >70 yrs.
  - BNP >1000 pg/mL
  - 24-hr fluid balance > 3L
  - Lower number units transfused

* Bosboom et al. Transfusion 2018;58(2):498-506
   Guangxi et al. Transfusion 2011;51(2):338-343
  o Roubinian et al. Transfusion 2017;57(7):1684-1690
TACO Warning Signs?

- Several studies have noted progressive alteration in vital signs during transfusion
- Andrzejewski and Popovský (2012) reported many reactions were associated primarily with mild changes in vitals
  - 97 TACO events were identified out of >16,000 transfused patients evaluated
  - Majority of these were associated with substantial increase in pulse, respiratory rate, and BP
  - Unexpectedly, 1/3 had ending Temp greater than 38C and 67% involved signs or symptoms related to febrile and/or inflammatory process

Gehrie et al Vox Sang. 2018 Feb;113(2):160-169
Hot TACO

- 927 transfusion reactions reviewed
- Disproportionate association with fever
- No association with patient or product age nor severity
- Suggestive of proinflammatory component?

TRALI

Comparison of Hemovigilance Definitions
A two-hit mechanism is believed necessary for a TRALI event

- Neutrophil sequestration and priming (1st hit)
  - Shift of neutrophils to state where they will be readily responsive to an activation signal
- Leukocyte activation (2nd hit)
TRALI

- 2004 Canadian Consensus Conference defined TRALI as new acute lung injury occurring within 6 hours of blood product administration
  - When a clear temporal relationship to an alternative risk factor for ALI/ARDS coexists, a formal diagnosis of TRALI cannot be made
  - The diagnostic terminology either "possible TRALI" or the more recently endorsed term "transfused ARDS" should be used

- Consensus group defined TRALI by its timing, hypoxemia, CXR findings, and the absence of evidence of circulatory overload caused by transfusion or preexisting cardiac condition

- TRALI is a clinical and radiographic diagnosis
  - Not dependent upon results of laboratory tests
<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALI during or within 6 hrs of TX, AND</strong></td>
<td><strong>New ALI present (all 5 criteria should be met):</strong></td>
</tr>
<tr>
<td><strong>Acute onset</strong></td>
<td></td>
</tr>
</tbody>
</table>
| **Hypoxemia defined by any of following:**  
- PaO2/FiO2 \(\leq 300\) mm Hg  
- Oxygen saturation < 90% on room air  
- Other clinical evidence AND | **Hypoxemia**  
- PaO2/FiO2 < 300mm Hg or  
- Oxygen saturation is < 90% on room air or  
- Other clinical evidence |
| **Radiographic evidence of bilateral infiltrate AND** | **Bilateral infiltrates on frontal chest radiograph** |
| **No evidence of left atrial hypertension (i.e. circulatory overload) AND** | **No evidence of left atrial hypertension (i.e. circulatory overload)** |
| **NO evidence of ALI prior to transfusion** | **No temporal relationship to an alternative risk factor for ALI during or within 6 hrs. of Tx** |
| | **Note: Possible TRALI same except for the presence of a temporal relationship to an alternative risk factor for ALI Clinical syndrome. Neither presence of donor anti-HLA or anti-HNA antibodies or recipient cognate antigen required for diagnosis.** |
Risk factors for Acute Lung Injury (ALI)

Direct lung injury
- Aspiration
- Pneumonia
- Toxic inhalation
- Lung contusion
- Near drowning

Indirect lung injury
- Severe sepsis
- Shock
- Multiple trauma
- Burn
- Acute pancreatitis
- Cardiopulmonary bypass
- Drug overdose
- *Brain injury – TBI, stroke
TRALI Risks

- Prospective surveillance of TRALI conducted at (UCSF), and Mayo Clinic, Rochester. 63,207 units of blood and blood components were transfused at the 2 centers, and 89 TRALI cases were identified.

Recipient Risk Factors

- Chronic alcohol abuse
- Positive fluid balance
- Peak airway pressure >30 cmH2O
- Shock
- Current smoker
- Liver surgery (transplant)
- IL-8 concentration

Other

- Female plasma
- Volume of units anti-HNA positive
- Quantity (plasma vol. x antibody strength) of cognate anti-HLA class II
  - Most frequent antibody implicated

TAD

Comparison of Hemovigilance Definitions
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute respiratory distress within 24 hrs of TX AND</td>
<td>Respiratory distress within 24 hrs of TX</td>
</tr>
<tr>
<td>Allergic reaction, TACO and TRALI definitions are not applicable</td>
<td>Does not meet criteria of TRALI, TACO or allergic reaction</td>
</tr>
<tr>
<td></td>
<td>Respiratory distress should be most prominent feature and not explained by underlying condition or any other known cause</td>
</tr>
</tbody>
</table>
TAD

- First appeared in literature in 2008 when European Hemovigilance Network introduced term
- Poorly understood entity
- Perceived as being clinically milder than TACO/TRALI
- Is it a residual on spectrum of TACO?
- Clearly, more to learn and understand on this entity
## A Tale of Two Cases

<table>
<thead>
<tr>
<th>59 year-old Female</th>
<th>27 year-old Male</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resection of gallbladder cancer and hepatectomy</strong></td>
<td><strong>Fractured vertebrae associated with a fall</strong></td>
</tr>
<tr>
<td>received 2 pRBC w/out issue. 2 days later critical, hypophosphatemia, suspected hyperammoniaemia.</td>
<td></td>
</tr>
<tr>
<td><strong>History of CABG and sleep apnea</strong></td>
<td><strong>History mild hypertension. No pre-existing lung disease or injury.</strong></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chest radiology several days prior to event: clear lungs and normal cardiac silhouette</strong></td>
<td><strong>Pre-event CT chest no changes in lungs or cardiac enlargement</strong></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Post-event CXR:</strong> perihilar, basilar pulmonary edema with alveolar filling, pulmonary venous hypertension and mild cardiomegaly</td>
<td><strong>Post-event new diffuse bilateral alveolar and parenchymal opacities. Heart size normal</strong></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Transfusion pRBC stopped after of 79mL due to dyspnea; Temp 98.3 to 100.1C; BP 136/69 to 128/67; HR 89 and 91; RR 26 to 31. Required intubation.</strong></td>
<td><strong>After transfusion pRBC, BP dropped by 40 sys, HR relatively unchanged, O2 90% with rapid increase in requirement in O2 support. Face mask</strong></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Volume status +6129 in prior 48 hours; Pro BNP = 3700 pg/ml after event</strong></td>
<td><strong>Volume status ~ +1600 No BNP available</strong></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Female donor, multiple pregnancies, HLA/neutrophil antibody negative</strong></td>
<td><strong>Male donor – <strong>positive</strong> for HLA Type II antibody; Patient HLA type unknown</strong></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TRALI unlikely cause. Temporal association with transfusion makes TACO more likely</strong></td>
<td><strong>Consistent with TRALI.</strong></td>
</tr>
</tbody>
</table>
Questions?

Thank You