TRALI & TACO

TNT, Triple A of Transfusion Medicine

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Statistics

• 1:1000 to 1:10,000 per blood product transfused
• 1:600 to 1:2500 per patient transfused
• Medicare records 2007 14.3 :100k, 2010 23.5:100k
  – Menis M et al. Transfusion 2014;54:2182-93
• Seen with all blood products but FFP is the riskiest, prior to all male plasma
• Seen in products with as little as 10-20ml of retained plasma if donor antibodies match patient antigen
• Cryo and IVIg may also cause it
Who’s at Risk?

• Prospective studies
  – 8% transfused ICU patients
  – 2.5% transfused cardiac surgery patients
  – Risk related to mechanical ventilation and increased pump time
    • Gajic O et al. Am J Respir Crit Care Med 2007;176:886-91
    • Vlaar AP et al. Crit Care Med 2010 38:771-8

• Medicare patient review – risk increases with:
  – Increased transfusions
  – Pulmonary fibrosis
  – Females
  – Smokers
Clinical Picture

• Sudden deterioration in lung function within 2-6 hours of transfusion
  – Tightness in chest, shortness of breath, cough
  – With or without fever and rigors
• Low O2 levels, hypotension, tachcardia,
• Crepitations on auscultation
• Copious frothy edema
Diagnostics

- Chest X-ray – bat wing pattern to total whiteout
- Pulmonary artery wedge pressure normal
- Hypotension unresponsive to fluids
  - 15% show hypertension
- Neutropenia followed by neutrophilia with class I HLA antibodies
- Monocytopenia with class II HLA antibodies
- May start to improve within 6 – 24 hours
Differential

• Diagnosis of exclusion
• Rule out other causes of acute lung injury
• Anaphylactic transfusion reaction
  – Bronchospasm and laryngeal edema
  – Erythema and urticaria, head, neck, trunk
• TACO – coming later in the lecture
• Bacterial contamination
  – Fever, hypotension, vascular collapse
  – Respiratory distress not a key symptom
Differential Diagnostic Flowchart

1. Dyspnea/Hypoxia within 6 hours of transfusion
   Transcutaneous O₂ sat < 90% or PaO₂/FiO₂ < 300 mm Hg
   
   - Yes
     - ?evidence of pulmonary edema
       - clinical or radiological
       
       - Yes
         - Is the edema cardiogenic/hydrostatic?
         
         - No
           - TRALI or ALI
             Other likely cause of ALI present?
             
             - No
               - Probable TRALI
                 Support respiration
                 Investigate donors
                 
             - Yes
               - ALI due to shock, sepsis, aspiration, etc + possible TRALI
                 Treat underlying condition and support respiration
                 Investigate donors if TRALI considered likely
                 
                 Factors increasing likelihood of TRALI:
                 New neutropenia or monocytopenia
                 Transfusion of plasma-rich components
                 Copious frothy yellow or pink tracheal exudate

   - No
     - Observe for further deterioration
     
     - Transfusion-related cause
       - eg. bronchospasm, anaphylaxis,
         Shock secondary to infected unit or ABO incompatibility
     
     - Non-transfusion related
       - eg. Infection
         Pulmonary embolus
         Myocardial infarct
     
     - Transfusion-related cardiac overload
       Prior cardiac failure
       Overhydration in renal failure
     
     - O₂ therapy and diuretics are indicated
     
     - Cardiac failure plus TRALI not excluded
Diagnostic Tips and Traps

• Shortness of breath, (SOB)
  – Transcutaneous O2 sat <90% room air
  – Arterial pO2 <60 mmHg
  – PaO2/FiO2 of less than 300 mmHg

• SOB with edema

• SOB without edema, think allergic reaction, shock due to bacterial contamination, ABO incompatibility, cardiac arrhythmia, infection, pulmonary embolus
To Be or Not To Be

• If the PaO2/FiO2 is less than 300mmHg, is it TRALI? Not necessarily.

• Cleveland Clinic 16,847 cardiac surgery patients

• Transfused patients had more risk adjusted pulmonary complications than non-transfused.

• Same of percentage of non-transfused and transfused patients had PaO2/FiO2 ratio less than 300mmHg, 65%.

• Conclusion: Ratio is diagnostic of lung injury but it can be unrelated to TRALI and may be due to nature of cardiac surgery
Diagnostic Traps

• SOB with edema, cardiac or not
  – X-ray
    • Trali – patchy, nodular, peripheral except for apices and costophrenic angles
    • Cardiac – Upper lobe distension, edema in perihilar and basal areas

• Left atrial pressure –
  – Trali - normal
  – Cardiac – elevated

• Echo to rule out cardiac dysfunction

• Inflammatory cytokines IL-6, IL-8 elevated prior to transfusion TRALI not TACO – first hit of 2 hits

• Anti-inflammatory IL-10 elevated prior to TACO – non-inflammatory hydrostatic edema\textsuperscript{A}.

A. Roubinian NH et. al. Transfusion 2015;55;1838-46
TRALI X-ray

CHF X-ray
X-rays

Figure 3: Chest radiographs of patients presenting with transfusion-related acute lung injury (TRALI)
Chest radiographs of two patients before (A, C) and after (B, D) onset of TRALI. Radiographs A and C show normal pulmonary vasculature with no signs of pulmonary oedema; B and D show infiltrative changes suggestive of pulmonary oedema. D shows the classic severe bilateral infiltrative changes that present with TRALI; however, frequently such changes are less apparent with chest x-rays, as shown in B.

Cardiac or Non-cardiac Edema

• B-type naturetic peptide
  – Trali - <250pg/ml
  – Cardiac – 2x previous level or >250pg/ml
  – Post:pre transfusion Bnp ratio <1.5 = TRALI
    • Zhou L et al. Transfusion 2005;45:1056-63
  – TACO >1000pg/ml NT-proBNP 93.8%sen/83.3%spec
  – >1923pg/ml NT-proBNP 87.5%sen/95.8%spec
    • Tobian et al. Transfusion 2008 Jun;48(6):1143-50
  – Other: too much overlap in BNP and NT-proBNP values in TACO and TRALI so no diagnostic significance
    • Li et al. Transfusion 2009 Jan;49(1):13-20

• Edema fluid - >70% serum protein = TRALI
Pulmonary Edema in TACO & TRALI

• Does etiology matter? Yes
• Mayo Clinic compared:
  – transfused critically ill patients with or without TRALI
  – transfused critically ill patients with or without TACO
• TRALI patients compared to their controls had statistically significant higher mortality rates for hospital, one year and two year periods.
• TACO patients compared to their controls did not have statistically significant higher mortality rates for hospital, one year and two year periods.
• Both TACO and TRALI patients had longer ICU and hospital lengths of stays than their respective controls
Canadian Consensus 2004

Table 56-2. 2004 Consensus Conference Definition of TRALI

I. TRALI criteria
   A. ALI
      1. Acute onset
      2. Hypoxemia
         a. Research setting:
            1) $\text{PaO}_2/\text{FiO}_2 \leq 300$, or
            2) $\text{SpO}_2 < 90\%$ on room air
         b. Nonresearch setting:
            1) $\text{PaO}_2/\text{FiO}_2 \leq 300$, or
            2) $\text{SpO}_2 < 90\%$ on room air, or
            3) other clinical evidence of hypoxemia
      3. Bilateral infiltrates on frontal chest radiograph
      4. No evidence of left atrial hypertension (ie, circulatory overload)
   B. No preexisting ALI before transfusion
   C. During or within 6 hours of transfusion
   D. No temporal relationship to an alternative risk factor for ALI

II. Possible TRALI
   A. ALI
   B. No preexisting ALI before transfusion
   C. During or within 6 hours of transfusion
   D. A clear temporal relationship to an alternative risk factor for ALI
# Acute Lung Injury & pTRALI Risk Factors

<table>
<thead>
<tr>
<th>ALI – Direct lung injury&lt;sup&gt;A&lt;/sup&gt;</th>
<th>pTRALI&lt;sup&gt;B&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspiration</td>
<td>Chronic alcohol abuse</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Current smoker</td>
</tr>
<tr>
<td>Toxic inhalation</td>
<td>Shock</td>
</tr>
<tr>
<td>Lung contusion</td>
<td>Positive fluid balance</td>
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<tr>
<td>Near drowning</td>
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</table>

| ALI – Indirect lung injury          |                   |
|-------------------------------------|                   |
| Severe sepsis                       |                   |
| Shock                               |                   |
| Multiple trauma                     |                   |
| Burn injury                         |                   |
| Acute pancreatitis                  |                   |
| Cardiopulmonary Bypass              |                   |
| Drug Overdose                       |                   |

**pTRALI** – new ALI within 6 hours of transfusion WITH alternate risk factor for ALI

Mortality rate pTRALI – 42%, similar to ALI

? pTRALI = Transfused ARDS<sup>C</sup>

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A. Kleinman S et al. Transfusion 2004;44:1774-1789  
C. Toy P et. al. Transfusion 2017;57(3);709-713
Raising the Index of Suspicion

• University of Cincinnati set up computer to generate an alert.
  • Alert based on Pa02/Fi02 is less than 300mmHg in a patient who was issued blood within 12 hours.
  • ICU rounds detected 9 of 14 patients requiring 2-3 hours of time
  • Computer detected 13 of 14 requiring 1-1.5 hours of time

Triggers for Reporting TRALI

• Survey of critical care physicians, hematologists, hemovigilance workers, transfusion medicine physicians using case vignettes and questionnaire.

• Positive indicators for reporting for all disciplines
  – Symptoms within one hour of transfusion
  – Transfusion of FFP
  – Absence of acute lung injury before transfusion

• Sepsis is a negative indicator for reporting

• Massive transfusion is a negative indicator for transfusion medicine physicians but a positive indicator for all others

• Critical care physicians trigger on massive transfusion and age of blood products

• Conclusion: Pre-transfusion inflammatory condition is a reason to withhold reporting and decision-making is different dependent on the specialty
  – Vlaar et al. Transfusion 2010 50(2) 443-51
New Syndrome

- Delayed TRALI Syndrome
- Acute lung injury 6-72 hours after transfusion
- Transfusion increases risk of ALI in critically ill patients, odds ratio 2.13
- Occurs in 25% of critically ill patients receiving transfusion
- 40% mortality rate

- Risk increases with number of transfusions
Pathophysiology

• Similar to ALI
• Interstitial and intralveolar edema
• WBCs outside capillary and in interstitial space and air spaces
• Increased wbc in capillaries adherent to wall
• WBC activation leads to endothelial damage and leakage of fluid into air spaces

Figure 56-2. Sections of lung from a fatal case of TRALI. Note the presence of granulocytes in the capillaries (arrow indicates neutrophils).
Two Step Theory

• 1\textsuperscript{st} Priming stimulus – may be underlying patient condition
• Activation of endothelium
• Causes stiffening, impedes flow through capillaries
• Causes prolonged contact with vessel wall leads to activation stimulus
• 2\textsuperscript{nd} activation stimulus – endothelial membrane receptors or HLA antibodies
• Causes release of granules leading to wall damage
• Allows linkage of fluid and wbc

Vlaar AP et al. Lancet 2013 382;984-94
Threshold Theory

- Trali can occur in healthy individuals
  - Brittingham study
- Threshold to cause reaction
  - Genetic predisposition with severe stimulation
  - Patient with co-morbidities and lesser stimulation
Antibodies

• 75-90% TRALI cases caused by donor HLA antibodies
• 20% type 1, 20% type 2, 40% both, 20% HNA
• Class 1 and HNA can bind to wbc to cause activation (A, B)
• Class 2 bind to moncytes which release cytokines to activate neutrophil (C)
• Rat model – Class 2 antigens expressed on PMN – inflammation, then transfused antibodies activate PMN^A
• Class 2 and HNA-3 antibodies have more potential to cause TRALI than Class 1^B. 
• Class 1, 2 and HNA bind to endothelium to sequester wbc and activate them^C (D)
• Cognate antigen – antibody match 1/3 to 1/2 suffer TRALI, dependent on strength and volume of antibody transfused

A. Kelher M. et. Al Transfusion 2016;56;3004-3011
B. Storch E et al. Blood 2014,124(12) pg. 1868-72
Mechanisms
Other Causes

• Patient antibodies – 10% of TRALI
  – Pt antibodies activate donor wbc, more likely to occur in multiparous females, multi-transfused patients, and transplants
  – Rarely interdonor TRALI – antibodies from one component react with antigens from another

• Bioactive lipids – polar and non-polar
  – Polar lyso-phosphatidylcholines, Platelet Activating Factor PAF attach to receptor on wbc causing priming – cause in autologous TRALI
  – Non-polar- arachidonic acid and HETE increase 5-20 fold 35 day blood, auto transfusion into volunteers 2 hours after injection with lipopolysaccharide to induce systemic inflammation (hit 1) did not induce mild TRALIA
    • BAL, CXR, LFT, PaO2/FIO2 ratio
  – CD-40 soluble ligand binds to its receptor on mono & neutros
  – Anti CD 36 antibodies may also cause TRALI
  – Hemin and neutrophil extracellular traps, new areas of researchB

A. Peters AL et. Al Vox Sang 2017,112:25-32
Treatment

- Respiratory support 02 to mechanical ventilation – 75% require short term
- Fluid support
- Vasopressors if fluids don’t work
- Diuretics and steroids don’t work
- Begin improvement in 6-24 hrs
- CXR shows clearance of edema 2-4 days
- Mortality 5-30% depending on underlying patient conditions though 40-50% is reported in severe patients
- Mouse study – lowered levels of IL-10 in TRALI, injection of IL-10 alleviated lung injury\(^A\)

Pediatric and Neonatal Populations

• Equivalent clinical picture as adults

• Dutch PICU – 4 year retro study 2294 patients, 304 transfused, 21 got TRALI 6.9% = adult ICU pts. L
  – None reported to BB
  – Mean time from start of transfusion to TRALI – 2 hrs.
  – Risk factors:

<table>
<thead>
<tr>
<th>Higher PRISM III score</th>
<th>Sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIC</td>
<td>Prior mechanical ventilation</td>
</tr>
<tr>
<td>Lower platelet count &lt;100</td>
<td>More positive fluid balance</td>
</tr>
</tbody>
</table>

  – No difference in number or type of components transfused
  – Mortality rate 76% TRALI vs. 11% transfused
  – Length of mechanical ventilation 183 hours vs. 25 hours

• Particular cause – directed donation by mother who has antibodies to child HLA

• Dad and child should not donate for mom either

A. Mulder HD et. al. Journal of Critical Care 2015(30);55-59
Lab/Donor Investigation

- Investigation takes time, donors are not captive
- Establish clinical diagnosis and treat
- Investigate donors of units transfused within 6 hours.
- Patient and donor should be HLA typed and all antibodies detected should be identified
  - Or HLA type patient and look for antibodies in donor
- Other selection by product type, plasma, platelet, cryo, rbc
  - Older protocol outdated due to AABB standards for male plasma, HLA antibody tested female platelet donors

Figure 56-7. Flow chart for investigation and management of donors.
Donor Management

• Deferring all involved donors excludes needlessly but some centers employ this strategy
  – Lookback study showed only 1/3 of patients receiving products from implicated HNA antibody donor had reaction though not TRALI.
  – Another study had 54 of 55 patients with matching antigens to donor antibody who received 109 products. No TRALI reported though other transfusion reactions were reported.

• Defer implicated donor from plasma-rich products

• Permanently defer donors with HNA-3 antibodies which is found in 95% of severe TRALI cases

• Untested donors may be flagged for examination of future transfusions.
Prevention of the 2\textsuperscript{nd} Trali Reaction

- Not much is reported on how to prevent a 2\textsuperscript{nd} trali reaction in a patient.
- Thought to be at higher risk for 2\textsuperscript{nd} reaction
- Judicious use of blood components
- Close monitoring before and after
- Fresh or washed products not shown to have a benefit
Who Has Antibodies?

- Most common in females with multiple pregnancies
  - Mom forms antibodies to fetal wbc's
  - 0 pregnancy, 2% females have antibody
  - 3 or more, 26.3% females have antibody
- Percentage also varies by time since last pregnancy with lower percentage with longer the time
- Frequency of HLA antibodies in men is less than 2%.
- These data based on EIA testing.
- Supports testing females with a history of pregnancy
  - Triulzi et al. Transfusion 2009 Sept;49(9):1779-82
- Transfusion less likely to cause antibodies
- Males 4-5% antibodies, nulliparous female – 10%
  - Sigle JP Vox Sang 2013 105:244-52
Prevention for Plasma

- Eliminate female FFP
- Use for cryo or recovered plasma
- Shift to FP24
- Hemovigilance studies in UK indicate 66% reduction when using male only FFP
- Use solvent detergent plasma
  - Antibodies neutralized by soluble antigens & dilution
  - Reduce use of FFP
- Use additive solution rbc to reduce plasma exposure
  - Transfusion 2008 Feb;48(2):393-7
  - Meta-analysis, of papers on male only plasma strategy
    - Decreased odds ratio 0.61 of TRALI
    - Decreased odds ratio 0.69 in 30 day mortality related to TRALI
      - Muller MCA et al. Transfusion 2015; 55:164-75
Prevention for Platelets

- Deferring multiparous women would reduce apheresis platelets by 550,000 per year
- Public health question, absolute safety vs availability for patients
- Blood centers increasing split components and male recruitment
- NYBC – testing females since 2009
- AABB standards as of October 2016 – previously pregnant females and pregnancy since last donation – Need HLA testing
TACO

- Hydrostatic edema - Occurs within 6 hours
- Hypoxemia - PaO2/FIO2 less than 90%
- Increased left atrial pressure with jugular vein distention, Pulmonary artery pressure >18mm, CVP > 12mm
- Elevation of BNP > 1.5 post – pre transfusion
- Tachycardia, Pedal edema, Pulmonary rales
- Hypertension with wide pulse pressure
- Cardiomegaly – cardio-thoracic ratio >0.53
- EKG changes - new ST segment elevation, T wave changes
- Fever may accompany 1/3 of cases

A. Parmar N et al. Vox Sang 2017;112:70-78
Incidence – Coming to a Patient Near You

- Median age 76, 2/3 cases >70+, 20% 60-69
- Thought to be 1:10,000
- More recognition – 1:5000 – 1:1000
- Electronic algorithm – review medical records, four academic medical centers – 1% of patients
- Retro review – 5% of non-cardiac surgical patients transfused in OR
- Requires more intensive hospital care, increases hospital stay, and 3x mortality
- SHOT 2016 – UK 6 years
  - 93 deaths
  - 39 were TACO

A. Roubinian NH et al. Vox Sang 2017;112(1):56-63
B. Clifford L et al. Anesthesiology 2015; 122:21-8
C. Murphy EL, Transfusion 2010; 50(Suppl 2):127A-8A
Causes – Not just Blood

• Positive fluid balance > 1 liter
  – TACO orthopedic patients – one institution – 2.5 liter positive prior to transfusion

• Transfusion rates > 200ml/hour

• Female

• History of: CHF, CRF, dialysis, recent surgery, mechanical ventilation, vasopressor use
  – Rana R et al. Transfusion 2006; 46:1478-83

• Two unit transfusions instead of 1

• Straw that breaks the camel’s back
Management

• Stop transfusion
• Oxygen
• IV Diuretics
• Place patient in sitting position

• PREVENTION IS THE KEY
• Be aware of risk factors in the patient
• Transfuse slower
• Give diuretics ahead of time
• Consider transfusing half units
## Table 17-6. Infusion Rates and Times for Adult Patients in Various Clinical Settings*

<table>
<thead>
<tr>
<th>Category Designation</th>
<th>Category Description</th>
<th>Potential Clinical Settings</th>
<th>Suggested Times or Rates of Infusion(^1)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Patient at severe risk for volume overload</td>
<td>Patients with CHF, COPD, ARF, severe anemia, or history of TACO (multiple episodes)</td>
<td>3.5 hours or 42 mL/hr to 2.5 hours or 60 mL/hr</td>
<td>All products issued in 0.5-unit increments so that 4-hr/maximum transfusion time is not violated</td>
</tr>
<tr>
<td>IB</td>
<td>Patient at risk for potential fluid overload</td>
<td>Patients with CHF, COPD, ARF, severe angina, or history of TACO (few episodes)</td>
<td>3.5 hours or 84 mL/hr to 2.5 hours or 120 mL/hr</td>
<td>Full units issued</td>
</tr>
<tr>
<td>II</td>
<td>Patient with minimal to no fluid overload concerns</td>
<td>Majority of patients requiring transfusion therapy</td>
<td>3.5 hours or 84 mL/hr to 2.5 hours or 120 mL/hr to 1.5 hours or 200 mL/hr</td>
<td>Full units issued</td>
</tr>
<tr>
<td>III</td>
<td>Patient in need of urgent fluid resuscitation</td>
<td>Patients with acute trauma and/or sudden massive blood loss</td>
<td>As fast as possible</td>
<td>Primarily for emergency and life-threatening situations</td>
</tr>
</tbody>
</table>

*Based on a focus study at Baystate Medical Center, Springfield, MA.

\(^1\)One unit of Red Blood Cells = 300 mL.

CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; ARF = acute renal failure; TACO = transfusion-associated circulatory overload.

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Transfusion Reactions 4th edition Mark Popovsky pg. 574
TNT Treatment

• Rx for Transfusion Service Physician
  – Antacids
  – Antianginals
  – Antiarrhythmics