Adverse Reactions to Transfusion: TRALI and TACO

Objectives

- Review the historical perspective and background of TRALI and TACO including definition of both
- Identify mechanisms of action, management, outcomes and prevention of both TRALI and TACO

Transfusion Related Fatalities by Complication, FY2009 through FY2013

TRALI: Historical Perspective

1950’s Description
- Acute hypoxemia and noncardiogenic pulmonary edema

1950 and 1960 Literature
- Document transfusion associated pulmonary edema without evidence of volume overload

1980’s
- Marked the emergence of a basic understanding of TRALI

1992
- 1st fatality reported to CBER

2000 to 2015
- 2000 TRALI represented 13% of all transfusions
- #1 cause of transfusion related fatalities
TRALI: Reports

**Fatalities**
- Majority of deaths associated with FFP
- Less frequent with RBCs, cryo, platelets and rare with IvIg

**Investigation**
- Donor antibody screens implicated multiparous females

**Non-Fatal Events**
- Reports by licensed blood establishments are on the increase
- Because of misdiagnosis and/or reporting the full scope of TRALI not known

TRALI: Immunologic Mechanism

Donor plasma contains Anti-HLA or Anti-Neutrophil antibodies that react with HLA or Neutrophil antigens on recipient leukocytes

Antibody-antigen complexes collect in the pulmonary microvasculature

Activation of complement cascade and/or mobilization of cytotoxic agents lead to acute lung injury in approximately 85% of cases

TRALI Non Immune Mechanism

Pre-existing condition activates neutrophils

Stored blood accumulates lipids and/or cytokines and upon transfusion activate the primed neutrophils

Activated primed neutrophils secrete toxic substances – may explain the 15% of cases where antibodies are not detected

TRALI Rates

Estimated incidence of TRALI is 0.014 – 0.08 %

- Rana et al Transfusion 2008;46:1478
  - 1 in 1271 Units TRALI
  - 1 in 534 units possible TRALI
  - 0.02% per unit of blood transfused
  - 0.16% per transfused patient

TRALI: Definition

- Hypoxemia (PaO2/FiO2 <300 or SpO2 < 90% on room air)
- Bilateral infiltrates on CXR
- No evidence of left atrial hypertension (i.e. TACO)
- No pre-existing acute lung injury before transfusion
- Acute onset - During transfusion or within 6 hours after transfusion
TRALI

- Common Signs and Symptoms
  - Dyspnea
  - Cyanosis
  - Hypoxemia
  - Fever (low grade)
  - Chills
  - Hypotension
  - Bilateral pulmonary edema (new onset)

TRALI: Diagnosis

- This is a clinical diagnosis plus supporting labs/images
- Diagnosis of exclusion: rule out other causes of transfusion associated respiratory distress
- Differential diagnosis
  - TACO (increased BP, I & O’s, BNP, diuresis helps)
  - Anaphylaxis (rash, wheezing)
  - Bacterial contamination (gram stain/culture)
  - Hemolytic transfusion reaction (type/screen/cross, DAT)

TRALI – Management

Respiratory Support

- Dictated by clinical picture
- Nasal cannula 2L to intubation

Diuretics

- Play no role in TRALI
- Pathology involves microvascular injury no fluid overload

TRALI Prevention: Donor Selection

AABB – Donor Centers

<table>
<thead>
<tr>
<th>Plasma containing products frequently implicated</th>
<th>Donors with antibodies should be deferred</th>
<th>Use of male plasma has reduced rates</th>
</tr>
</thead>
</table>

- AABB Standard 5.4.1.2
  - Plasma and whole blood for allogeneic transfusion shall be from males, females who have not been pregnant or females who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies

TRALI – Risk Reduction

Transfusion Centers

<table>
<thead>
<tr>
<th>Washed Cellular Products</th>
<th>Pre-storage Leukoreduction</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Expensive, time consuming</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Small amounts of plasma can cause TRALI in-vivo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Not effective in inhibiting BRM mediated TRALI in-vivo
- In Norway – no TRALI reported in the use of solvent-detergent plasma
Transfusion Related Acute Lung Injury (TRALI)

- Preventive Measures:
  - American Red Cross TRALI Mitigation:
    - Defer donors implicated in a TRALI reaction
    - All transfusable plasma
    - from male donors
    - Women who report a history of no pregnancy
    - Females who have been tested and found to have an acceptably low level of HLS antibodies

- Hospital:
  - Minimize the inappropriate transfusion of blood products
  - Minimize AB plasma utilization; group specific plasma should be given when time permits.

Note: Avoidance of discard is not an indication for use.

TRALI Outcomes

- Mortality varies
- Reported between 5% & 25%
- 80% recover quickly
- Between 24 to 72 hours

Immediate steps to take when an adverse reaction to transfusion is suspected

1. Recognize
2. Stop
3. Assess
4. Notify
5. Treat
6. Report
7. Document

TRALI – Recommendations

Be alert to respiratory distress
Immediately discontinue transfusion
Begin oxygen and supportive therapy
Follow your routine notification sops
Transfusion Service will notify the Blood Center
### Possible Clinical Interventions

<table>
<thead>
<tr>
<th>Reaction Type</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile Non-Hemolytic</td>
<td>Antipyretics</td>
</tr>
<tr>
<td>Septic</td>
<td>Antipyretics, Analgesics</td>
</tr>
<tr>
<td>Anaphylactic</td>
<td>Antipyretics, Analgesics, Broad spectrum antibiotics, Blood cultures</td>
</tr>
<tr>
<td>TRALI</td>
<td>Oxygen, Intubation, Anti-histamines, Corticosteroids, Beta 2 agonists</td>
</tr>
<tr>
<td>TACO</td>
<td>Oxygen, Feet up, Fluids, Epinephrine, Intubation, Anti-histamines, Chest x-ray, Benzodiazepines, Beta 2 agonists</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Oxygen, Antipyretics, Intubation</td>
</tr>
<tr>
<td>Septic Shock</td>
<td>Oxygen, Antipyretics, Intubation</td>
</tr>
<tr>
<td>Respiratory Distress</td>
<td>Oxygen, Antipyretics, Intubation</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Oxygen, Antipyretics, Intubation</td>
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### TRALI: Common Question

**Question:** Can a patient be transfused after a TRALI reaction?

**Answer:** Yes.

- The reaction is an issue with the donor, not the patient.
- Once the transfusion reaction workup has been done and hemolysis is ruled out, the patient may be transfused again.

### TRALI: Reporting

- Fatalities from TRALI should be reported to CBER in accordance with 21CFR606.170(b).
- FDA encourages voluntary reporting of TRALI as a serious adverse reaction to transfusions.

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<tr>
<td>Express Mail</td>
<td>MedWatch HF-2, 5600 Fishers Lane, Rockville, MD 20852</td>
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### Transfusion Related Fatalities by Complication, FY2009 through FY2013

<table>
<thead>
<tr>
<th>Complication</th>
<th>Number of Fatalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRALI</td>
<td>20</td>
</tr>
<tr>
<td>HTS (ABO, Rh)</td>
<td>16</td>
</tr>
<tr>
<td>Endotoxin (Sepsis)</td>
<td>11</td>
</tr>
<tr>
<td>TACO</td>
<td>14</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>11</td>
</tr>
<tr>
<td>Other</td>
<td>20</td>
</tr>
</tbody>
</table>

### TACO History

**Historical Information**

- Physicians have known transfusion is a risk factor for circulatory overload.
- TACO is now taken seriously.
- Rediscovered now that TRALI is a major focus.
- Clinical impact recognized to be more than giving supplemental oxygen and a dose of diuretics.
Massachusetts Medicare Study
- Popovsky demonstrated TACO patients required more intensive care and longer length of care

FDA Data Demonstrate
- TACO is the second most common cause of death from transfusion

Fiscal 2005-2006
- Fatal case reports increased from 2-13% of all fatalities

French Hemovigilance
- 6 year period 742 cases identified resulting in 27 deaths

US Biovigilance Program
- Undoubtedly more fatalities identified

TACO Mechanism
- Inability of circulatory system to tolerate volume or rate of transfusion
- "Cardiogenic pulmonary edema"
- ANY patient may get TACO – especially if transfused rapidly

TACO Rates
- 3. Rana et al Transfusion 2006; 46:1478

- 0.03%-8% of transfusions depending on criteria
- TACO occurred in 1 of 356 transfusions

TACO
- Patients with the following are most at risk:
  - Diminished cardiac reserve
  - Renal failure or dysfunction
  - Older (85% occur in patients greater than age 60)
  - Younger (smaller total blood volume)
  - Chronic anemias (e.g. sickle cell, thalassemias)
  - Those receiving large amounts of blood products in a short time frame OR receiving double red cell transfusions

Transfusion Associated Circulatory Overload (TACO)
- Definition:
  - Infusion volume that cannot be effectively processed by the recipient either due to high rate and/or volume of infusion or an underlying cardiac or pulmonary pathology.
  - Can occur after only a few ml up to 6 hrs after
  - Fairly Common → occur in ~1-8% of transfusions
TACO: Diagnosis

- Physical exam: lung crackles, rales, elevated JVP, S3 gallop
- Chest XR: Alveolar and interstitial edema, Kerley B lines, pleural effusions, cardiomegaly
- Elevated BNP
- Non-immune mediated, so no antibodies

TACO: Signs/Symptoms

- Shortness of breath, cough, chest tightness (from fluid accumulation in the lungs)
- Headache (from the increased systolic pressure)
- Most typically towards the end of transfusion or shortly afterwards when the maximum amount of fluid was transfused

Transfusion Associated Circulatory Overload (TACO)

- Common Signs and Symptoms
  - Dyspnea
  - Pulmonary edema
  - Tachycardia
  - Orthopnea
  - Cyanosis
  - Headache
  - Chest tightness

TACO: Management

- Stop the transfusion
- Follow your facilities routine procedures for adverse reactions
- Evaluate the patient (you may want to sit the patient upright to minimize fluid accumulation in the lungs)
- Give supplemental oxygen
- Diuretics to decrease the blood volume
- Severe cases may require therapeutic phlebotomy though typically patients respond to supportive therapy

Possible Clinical Interventions

TACO: Prevention

- Control rate of infusion (suggest: 1 mL/Kg/hour)
- Split units in half or use aliquots
- Consider lower volume units, or reduced volume units
- Some suggest simultaneous administration of furosemide
- "critical care level" nursing supervision in high-risk patients
TACO Outcomes

One study showed the following:

- 18% (n=98) of pts required transfer to ICU
- 8% suffered a major complication
- 2% died

Early recognition better clinical outcomes

TACO: Outcomes

- Andrzejewski and colleagues found at 15 minutes after transfusion, systolic blood pressure, pulse pressure, and mean arterial pressure were significantly higher in fluid-challenged patients than those not overloaded
- These patients could benefit from bedside monitoring

TACO: Reporting

- Report to blood bank as a possible transfusion reaction so the proper investigation may begin
- Contemplate differential diagnosis and encourage appropriate patient care, laboratory analysis, or other diagnostic measures
- Document all details for the EMR and blood bank

TACO: Follow-Up

- Ask patients if they have any history of previous transfusion reactions and if so, to please describe
- Clinical follow-up—the outcome varies with overall clinical status of the patient so clinical correlation is recommended to decide upon what time frame to follow up with the clinician
- Ensure all elements are documented

TRALI or TACO: Fatality

- When the death of a patient is a result of a transfusion reaction or a complication related to a transfusion current good manufacturing practice (cGMP) regulations require reporting of the fatality to the FDA by the facility that performed the compatibility testing.
- The patient’s underlying illness may make determination of the cause of death difficult.
- If there is any clinical suspicion that the transfusion may have contributed to the patient’s death, an investigation into that possibility should be performed

TRALI or TACO: Reporting

- Fatalities from any transfusion should be reported to CBER in accordance with 21CFR606.170(b)
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### TRALI vs. TACO

<table>
<thead>
<tr>
<th>Feature</th>
<th>TRALI</th>
<th>TACO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Temperature</td>
<td>Fever can be present</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>Hypotension</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Respiratory Symptoms</td>
<td>Acute dyspnea</td>
<td>Acute dyspnea</td>
</tr>
<tr>
<td>Neck Veins</td>
<td>Unchanged</td>
<td>Can be distended</td>
</tr>
<tr>
<td>Auscultation</td>
<td>Rales</td>
<td>Rales, 53 may be present</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Diffuse bilateral infiltrates</td>
<td>Diffuse bilateral infiltrates</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>Normal, decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>PA auscultation pressure</td>
<td>16 mmHg or less</td>
<td>Greater than 16 mmHg</td>
</tr>
<tr>
<td>Pulmonary edema fluid</td>
<td>Tranudate</td>
<td>Transudate</td>
</tr>
<tr>
<td>Fluid balance</td>
<td>Positive, even, negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Response to diuretic</td>
<td>Minimal</td>
<td>Significant</td>
</tr>
<tr>
<td>White count</td>
<td>Transient leukopenia</td>
<td>Unchanged</td>
</tr>
<tr>
<td>BNP</td>
<td>≤300 pg/mL</td>
<td>&gt;1200 pg/mL</td>
</tr>
<tr>
<td>Leukocyte antibodies</td>
<td>Donor leukocyte antibodies present, crossmatch incompatibility between donor and recipient</td>
<td>Donor leukocyte antibodies may or may not be present, positive results can suggest TRALI even with true TACO cases</td>
</tr>
</tbody>
</table>

### Conditions That Mimic Transfusion-Related Acute Lung Injury With Symptoms and Circumstances That Help Distinguish Them

- **Acute circulatory (volume) overload**
  - High-volume fluid infusion or transfusion over a short period
  - Elderly or very young patient
  - Increase in systolic blood pressure
  - Pre-existing chronic volume overload state (e.g.: renal failure, congestive heart failure)
  - Severe chronic anemia
  - Cardiomegaly on chest x-ray
  - Rales on pulmonary auscultation
  - Distended pulmonary artery on chest x-ray
  - Response to diuresis

- **Pulmonary embolism**
  - Hypercoagulable state (e.g.: pregnancy, known thrombocytopenia syndrome)
  - Hypercoagulable state (e.g.: pregnancy, known thrombocytopenia syndrome)
  - Malignancy
  - Distended pulmonary artery on chest x-ray
  - No or little pulmonary edema on chest x-ray

### TRALI vs. TACO

- Which of the following is not included in the diagnosis of TACO?
  - A. Elevated JVP
  - B. Increased or new pulmonary edema
  - C. Antibodies to HLA or neutrophils
  - D. Increased BNP
  - E. Cardiomegaly

- Which of the following is not included in the management of TACO?
  - A. Diuretics
  - B. Oxygen
  - C. Hold off on future transfusions for a while
  - D. Sitting upright
  - E. Vasopressors
TRALI vs. TACO

Which of the following is NOT a symptom of TACO?
A. Dyspnea
B. Back pain
C. Cough
D. Chest tightness
E. Hypertension

Which of the following does not support the diagnosis of TRALI?
A. Bilateral infiltrates on CXR
B. Symptoms typically begin 1-2 hours after transfusion and are fully manifest within 1-6 hours
C. Transient leukopenia, neutropenia, monocytopenia, hypocomplementemia
D. Decreased BP in response to diuretics
E. Frothy pink secretions from ETT

Which of the following is not included in the investigation or prevention of TRALI?
A. Determine if donor has HLA or neutrophil antibodies
B. Determine if recipient has corresponding antigen to donor antibodies
C. Remove implicated donor from donor pool
D. Universal leukoreduction of donor products
E. Transfuse male donor-only plasma

Which of the following is not included in the definition of TRALI?
A. Hypoxemia
B. Occurring 24 hours after transfusion
C. Bilateral infiltrates on chest XR
D. No pre-existing acute lung injury before transfusion
E. No evidence of TACO

Which of the following is not included in the proposed mechanisms for TRALI?
A. Gram negative cocci
B. Anti-HLA antibodies
C. Anti-neutrophil antibodies
D. Biologically active lipids
E. Cytokines

Adverse Reaction Case Studies
Case Study – Patient History

- 67 year old female with a history of multiple myeloma and TTP
  - Plasma exchange scheduled for next morning
- Transfusion service order received
  - Type & Screen
  - 4000 mL plasma

Transfusion Services Result History

<table>
<thead>
<tr>
<th>Previous History</th>
<th>Current Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>B positive</td>
<td>B positive</td>
</tr>
<tr>
<td>Nonreactive Antibody Screen</td>
<td>Nonreactive Antibody Screen</td>
</tr>
<tr>
<td>History of multiple RBC and plasma transfusions</td>
<td>16 units B positive plasma prepared</td>
</tr>
</tbody>
</table>

Transfusion Event

- The plasma exchange was completed and transportation was called to return the patient to the room, when the patient said she did not feel well. She complained of shortness of breath.
- An adverse reaction to the plasma was suspected
  - Patient's Physician was paged
  - Transfusion Service was called

Transfusion Event Timeline

- Post-transfusion nursing clerical check OK:
  1) Product label
  2) Product tag
  3) Patient armband

- Patient first/last name
- Unique identification number
- Blood unit number
- ABO/Rh

The nurse sent the following to the lab for investigation…

- all paperwork
- the bags from all 16 units of plasma
- administration set

Adverse Reaction- Laboratory Investigation

- No abnormalities
- All accompanying IV solutions compatible
Adverse Reaction- Laboratory Investigation

- Post-transfusion laboratory clerical check OK:
  1) Patient armband
  2) Product tag
  3) Product label
  - Patient first/last name
  - Unique identification number
  - Blood unit number
  - ABO/Rh

Clerical check
Inspect product

Patient's Pre-transfusion specimen is clear and there is no evidence of hemolysis or icterus

Patient's Post-transfusion specimen is clear and there is no evidence of hemolysis or icterus

Adverse Reaction Signs and Symptoms: REVIEW

- Pre-transfusion Specimen
  - B positive
  - Nonreactive Antibody Screen
  - Polyspecific DAT nonreactive

- Post-transfusion Specimen
  - B positive
  - Nonreactive Antibody Screen
  - Polyspecific DAT nonreactive

Clerical check
Compare specimens
Inspect product

Laboratory investigation:
- Clerical check (lab/nursing) identical
- No visual hemolysis—serum or urine
- Pre- and post- sample testing identical
- DAT nonreactive

<table>
<thead>
<tr>
<th>Test</th>
<th>Pre-FFP transfusion</th>
<th>15 min Post-FFP transfusion</th>
</tr>
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<tbody>
<tr>
<td>Blood Pressure</td>
<td>138/84</td>
<td>139/83</td>
</tr>
<tr>
<td>Pulse (beats/minute)</td>
<td>88</td>
<td>99</td>
</tr>
<tr>
<td>Respiration (breaths/minute)</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Temperature (°F/°C)</td>
<td>98.6</td>
<td>98.7</td>
</tr>
</tbody>
</table>

Dyspnea and felt unwell

Adverse Reaction: Transfusion Event

- After this x-ray was taken:
  - Patient required Oxygen
    - Oxygen saturations 85% on 2L nasal cannula
  - Patient was subsequently intubated and admitted to the ICU
  - Patient condition continued to deteriorate
  - Patient expired on day 4

Chest X-Ray

Normal
Patient

American Red Cross
Reaction Follow-Up

- TRALI reaction reported to blood supplier
  - Patient received 16 units of thawed plasma exhibiting a reaction within 6 hours
- Blood Supplier
  - Determined 4 of 16 donors were at ‘risk’ for developing HLA antibodies
    - All 4 ‘suspect’ donors were tested for HLA antibodies
    - One donor tested positive for HLA Granulocyte Class I and II antibodies
      - This donor was permanently deferred

Summary

- TRALI and TACO have been documented for several decades
- In the event of a transfusion reaction, the first thing to do is stop the transfusion
- Prevention is best, but also recall that early recognition leads to better clinical outcomes
- Understanding the profiles of TRALI versus TACO can not only expedite appropriate patient care but also helps the blood bank and blood provider be aware of transfusion-related complications

References

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- Andrzejewski CA, Popovsky MA, Deit T. Measured and derived vital sign changes in transfusion reactions associated with fluid challenges. Transfusion 2008;48 Suppl:204
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