Transfusion Related Acute Lung Injury: What’s new?

Saudi Society of Hematology Congress

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Disclosures

• I have no conflicts of interest to disclose.
Objectives

• To review definition of TRALI and updated definition of ARDS
• To describe newly identified role of platelets and neutrophil extracellular traps (NETs)
• To outline TRALI mitigation strategies and their effectiveness
Transfusion related acute lung injury

• TRALI is serious transfusion complication
• One of the leading causes of transfusion related mortality
• First described in 1985
NHLBI Consensus Definition 2004

Acute lung injury (ALI)

- Acute onset
- \( \text{PaO}_2/\text{FIO}_2 < 300 \text{ mm Hg} \), or worsening of \( P_{\text{A}} \) to \( F \) ratio
- Bilateral infiltrative changes on chest radiograph

Temporal relationship to transfusion (6 hr)

No volume overload

No other risk factor for ALI

Suspected TRALI

Transfusion 2004; 44: 1774–89.
NHLBI Consensus Definition 2004

Acute lung injury (ALI)

Temporal relationship to transfusion (6 hr)

No volume overload

Another risk factor for ALI present

Possible TRALI

• Acute onset
• $\text{PaO}_2/\text{FIO}_2 < 300 \text{ mm Hg}$, or worsening of $\text{P}_\text{a} \text{ to F ratio}$
• Bilateral infiltrative changes on chest radiograph

Transfusion 2004; 44: 1774–89.
Berlin definition of ARDS

• No longer an entity named acute lung injury (ALI)
• ARDS is categorized into
  • Mild PaO2/FiO2 200-300 mmHg
  • Moderate PaO2/FiO2 200-100 mmHg
  • Severe PaO2/FiO2 <= 100 mm Hg

Incidence of TRALI

<table>
<thead>
<tr>
<th>Study type and inclusion</th>
<th>Population</th>
<th>Country</th>
<th>Study year</th>
<th>Incidence of TRALI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Per patient transfused</td>
</tr>
<tr>
<td>Popovsky et al$^{24}$</td>
<td>Retrospective, active</td>
<td>Hospital</td>
<td>USA</td>
<td>1983</td>
</tr>
<tr>
<td>Henderson et al$^{22}$</td>
<td>Retrospective, passive</td>
<td>Regional</td>
<td>Australia</td>
<td>1981-89</td>
</tr>
<tr>
<td>Clarke$^{13}$</td>
<td>Retrospective, passive</td>
<td>Hospital</td>
<td>USA</td>
<td>1994</td>
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<tr>
<td>Silliman et al$^{22}$</td>
<td>Retrospective, active</td>
<td>Hospital</td>
<td>Canada</td>
<td>1991-95</td>
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<tr>
<td>Wallis et al$^{24}$</td>
<td>Retrospective, passive</td>
<td>Hospital</td>
<td>UK</td>
<td>1991-2003</td>
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<tr>
<td>Wiersum-Osselton et al$^{24}$</td>
<td>Retrospective, passive</td>
<td>National</td>
<td>The Netherlands</td>
<td>2002-05</td>
</tr>
<tr>
<td>Rana et al$^{25}$</td>
<td>Retrospective, active</td>
<td>ICU</td>
<td>USA</td>
<td>2003</td>
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<tr>
<td>Vlaar et al$^{28}$</td>
<td>Retrospective, active</td>
<td>ICU</td>
<td>The Netherlands</td>
<td>2004-07</td>
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<tr>
<td>Gajic et al$^{29}$</td>
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<td>ICU</td>
<td>USA</td>
<td>2005-07</td>
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<tr>
<td>Benson et al$^{26}$</td>
<td>Retrospective, active</td>
<td>ICU</td>
<td>USA</td>
<td>2002-08</td>
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<tr>
<td>Vlaar et al$^{35}$</td>
<td>Prospective, active</td>
<td>ICU</td>
<td>The Netherlands</td>
<td>2006-09</td>
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<tr>
<td>Toy et al$^{10}$</td>
<td>Prospective, active</td>
<td>Regional</td>
<td>USA</td>
<td>2006-09</td>
</tr>
</tbody>
</table>

TRALI=transfusion-related acute lung injury. ICU=intensive-care unit. *Incidence identified only in plasma products transfused. †Incidence identified only in products of platelet concentrates transfused.
TRALI is a clinical diagnosis

- Dyspnea
- Tachypnea
- Hypoxemia
- Rigors
- Fever
- Tachycardia

- Hypothermia
- Hypotension
- Hypertension
- Transient leukopenia
- Transient thrombocytopenia
TRALI is a clinical diagnosis

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Remind clinicians that TRALI cannot be diagnosed without:

- Documentation of volume status
- Chest X-ray
- Evidence of hypoxemia
Confirmation of the diagnosis

• No tests to confirm

• HLA and HNA antibodies testing of the donor are done to evaluate further eligibility to donate, but results do not necessarily affect the diagnosis

• HLA or HNA antibodies can be detected in 50-80% of donors implicated in TRALI cases

Vox Sang 2016; 111:71–78
Prognosis

• TRALI ranges from mild to severe
• 5-10% of patients with TRALI die
• That is much lower than deaths related to other causes of ARDS (30–40%)

• Management is supportive
Pathophysiology

• 2-hit theory
• First hit: a susceptible (primed) recipient
• Second hit: passive transfusion of
  • HLA/HNA antibodies, or
  • Bioactive lipids, or
  • Soluble CD40 ligand (sCD40L), or
  • Aged RBCs
High IL-8 levels

First hit
- Septic
- Haematological malignancy
- Massive blood transfusion
- Chronic alcohol abuse
- Older age
- Shock
- Acute renal failure
- Severe liver disease
- Trauma
- Cardiac surgery
- Spinal surgery
- Liver surgery
- Mechanical ventilation

Second hit
- HLA class I antibodies
- HLA class II antibodies
- HNA antibodies
- Aged cellular transfusion products
• How can TRALI be explained in patients who are previously healthy?
Threshold model
Role of platelets

• Platelet sequestration in the lungs is observed in animal models of ALI
• This phenomena is dependant on the presence of neutrophils
• Platelets and neutrophils aggregate in blood vessels and around alveoli

J Clin Investig 2009; 119:3450–3461
In animal models

- Platelet depletion led to protection from lung injury
- Aspirin led to reduced pulmonary edema and improved survival.

Can aspirin prevent/stop TRALI in humans?

In a case control study of 109 TRALI cases, use of aspirin was not protective.

Anaesthesia 2012; 67(6): 594-599
Prevention or Treatment of Ards With Aspirin: A Review of Preclinical Models and Meta-Analysis of Clinical Studies

Fig. 2. Forest plot of estimated associations between aspirin (ASA) use and adverse clinical outcomes in patients at risk of acute respiratory distress syndrome (ARDS) or transfusion-associated acute lung injury (TRALI) or with established ARDS.
The role of neutrophil extracellular traps ‘NETs’

• NETosis: activated neutrophil nuclear DNA is released in long chromatin filaments that form web-like structures decorated with granular proteins.


Blood 2012 120:1152-1154;
The role of NETs in TRALI

- Activated platelets induce NET formation in vitro
- NETs increase endothelial permeability
- NET formation in TRALI is a fast event after antibody challenge

In animal models

• Aspirin blocks NET formation and platelet sequestration in TRALI
• Interventions targeting NETs (DNase / Histone antibodies) reduced complications of TRALI and improved survival

Risk mitigation

• Proper use of blood components

• Elimination of high risk donors
  • Investigated after a case of TRALI
  • Based on history of pregnancy
Prevalence of HLA antibodies in donors

• Baseline rate of HLA antibody is similar in men and women with no exposure (around 2%)
• Transfusion history is not a risk factor for development of HLA antibodies in men (1 vs. 1.7% transfused)
• 17.5% of women overall have HLA antibodies, depending on pregnancy history

Triulzi et. Al. Transfusion 2009; 49:1779-82
# Prevalence of HLA antibodies in donors

<table>
<thead>
<tr>
<th>Number of pregnancies</th>
<th>Percentage with HLA antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.7%</td>
</tr>
<tr>
<td>1</td>
<td>11.2</td>
</tr>
<tr>
<td>2</td>
<td>22.5</td>
</tr>
<tr>
<td>3</td>
<td>27.5</td>
</tr>
<tr>
<td>4 or more</td>
<td>32.2</td>
</tr>
</tbody>
</table>

Triulzi et. Al. Transfusion 2009; 49:1779-82
AABB 29th BBTS standards (2014)

• “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 Mitigation Strategies

<table>
<thead>
<tr>
<th></th>
<th>RBCs</th>
<th>Platelets</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deferral of donor implicated in TRALI</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Limiting donation to males or females who were never pregnant or who are antibody negative</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Solvent detergent (pooling)</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Filter (experimental)</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BLOOD 2014;123,(22)  
Lancet 2013; 382: 984–94
Pre- and post-TRALI mitigation factors: Number of TRALI cases per product distributed/transfused. The platelethpheresis product risk reduction shows pre- and postimplementation of products from males or nulligravida or HLA-antibody-negative parous females per New York Blood Center data. The current risk for the RBC product is per New York Blood Center data. The arrow shows potential risk reduction with use of an experimental filter. The left-most plasma product risk reduction shows pre- and postimplementation of products from males or nulligravida females per New York Blood Center data. The right-most plasma product risk reduction shows pre- and postimplementation of solvent detergent products per French Agency for the Safety of Health Products data.
Conclusions

• ALI is now mild ARDS
• The role of platelets and NETs is being emphasized in TRALI events
• Multiple TRALI mitigation strategies exist with good effect
Thank you