Transfusion Related Acute Lung Injury (TRALI) – an update from Canadian Blood Services

HLA/HPA Matched Platelet Programme – “Making it Great Again”

Vein to Vein conference March 17, 2017

D. K. Young
MD, FRCPC (Anesthesia)
Disclosures:

• Employee of Canadian Blood Services
• Chair of TRALI Medical Review Group (TMRG)
• Medical lead for HLA/HPA platelet programme consolidation
TRALI: Epidemiology

- 0.4 to 1.6 cases per 1,000 patients transfused
  - Likely under-reported and under-recognized
- Described with all blood products
  - Usually contain > 60 mL plasma
- US FDA observed TRALI to be the leading cause of transfusion related deaths 2008-2012.
  - Responsible for 37% of transfusion-related mortalities
  - Highest cause of transfusion-related morbidity (TRALI and possible TRALI)

TRALI: Pathophysiology

**Immune**

- Passive transfer of donor alloantibodies in plasma of transfused product
  - Anti-HLA (Class I)
  - Anti-HLA (Class II)
  - Human neutrophil antigens (HNA)
- Antibody binding to circulating WBC (and perhaps also pulmonary endothelium) causes cellular activation
TRALI: Pathophysiology

Non-immune

- TRALI is also caused by the infusion of “biologic response modifiers” within the blood component
  - Cytokines (IL-6, IL-8, IL-1, TNF-α)
  - Lipids with neutrophil-priming activity
  - CD40 ligand
- These substances accumulate in cellular blood products with prolonged storage

Silliman CC et al., Transfusion 1997
Silliman CC et al., Blood 2003
TRALI: Clinical presentation

- Virtually all patients have:
  - Shortness of breath
  - Hypoxia
  - Bilateral lung infiltrates on CXR
- May also have:
  - Hypotension, fever, transient leukopenia
- Other:
  - Chest findings on auscultation tend to be minimal
  - No evidence of circulatory overload

Bux and Sachs. Transfusion Medicine and Hemotherapy. 2008
TRALI: Diagnosis

• Clinical diagnosis
  – No test with which to diagnose TRALI.

• TRALI should be suspected if a patient has appropriate clinical findings within six hours of a transfusion

• Exclude of other causes of pulmonary edema
  – Cardiac causes
  – Volume overload
Definition of TRALI

- During or within 6 hours of transfusion
- Acute lung injury
  - Acute onset
  - Hypoxemia
    - \( \text{PaO}_2/\text{FiO}_2 \leq 300 \)
    - \( \text{SpO}_2 < 90\% \text{ on room air} \)
  - Bilateral infiltrates on CXR
  - No evidence of circulatory overload (PCWP \( \geq 18 \))
- No preexisting ALI
- No temporal relationship to an alternate risk factor for ALI

Kleinman et al. Transfusion 2004;44:1774-89
Definition of Possible TRALI

- ALI
- No preexisting ALI before transfusion
- During or within 6 hours of transfusion
- A clear temporal relationship to an alternative risk factor for ALI
## Alternate risk factors for ALI

<table>
<thead>
<tr>
<th>Direct lung injury</th>
<th>Indirect lung injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspiration</td>
<td>Severe sepsis</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Shock multiple trauma</td>
</tr>
<tr>
<td>Toxic inhalation</td>
<td>Burn injury</td>
</tr>
<tr>
<td>Lung contusion</td>
<td>Acute pancreatitis</td>
</tr>
<tr>
<td>Near drowning</td>
<td>Cardiopulmonary bypass</td>
</tr>
<tr>
<td></td>
<td>Drug overdose</td>
</tr>
</tbody>
</table>

**Diagnosis and definition of TRALI**

Kleinman et al. Transfusion 2004;44:1774-89
TRALI Risk Mitigation Strategies: 1º Prevention

- Predominantly male plasma for transfusion
  - October 2007
- Predominantly male plasma in pooled platelets with roll-out of buffy coat method
  - 2005-June 2008
- Predominantly male apheresis platelets
  - July 2009
- Transfuse only when necessary
TRALI Risk Mitigation Strategies: 2º Prevention

• Canadian Blood Services investigates TRALI reactions to facilitate 2º prevention of TRALI reactions
• Donors who are implicated in TRALI reactions are removed from the donation pool so they do not cause further reactions
• This process is not for patient management
  – TRALI diagnosis is a clinical diagnosis
  – Management of TRALI occurs at the time of reaction, results of testing of donors will be delayed
• Do not submit reactions to “rule out TRALI” if you don’t think that is what is going on
Different Perspectives

Hospitals

- Cause – illness +/- treatment +/- transfusion
- TRALI - Clinical dx – likely multifactorial and not mutually exclusive
- No diagnostic test available

Canadian Blood Services

- Cause – want to be sure it is the transfusion and not a confounder
- Donor - is donor unsafe for recipients
- Test for safety – identify and remove potentially unsafe donors
- Avoid testing donors not implicated in TRALI reactions
- Global perspective

Slide modified from Dr. Barbara Hannach
What happens when a TRALI reaction is reported to Canadian Blood Services?
TRALI Risk Mitigation Strategies: 2º Prevention

- All adverse events where TRALI is considered are reported to the TRALI Medical Review Group (TMRG)
- TMRG reviews event to ensure that it meets the Consensus Conference definition for TRALI or possible TRALI
- Group may label reaction as “TRALI inconclusive”
  - Used when reaction likely meets definition for TRALI or possible TRALI, but information provided is incomplete
    - Examples:
      - No assessment of fluid balance performed
      - Not provided with $SaO_2$ or $PaO_2$ measurements
TRALI and Canadian Blood Services

TRALI Patient Data Form completed by

Hospitals

Hospital Customer Forms
TRALI Risk Mitigation Strategies: 2º Prevention

• Important that all relevant clinical information is provided when reporting TRALI reactions

• Very difficult to differentiate between TRALI, TACO, TAD and other causes of transfusion-associated dyspnea when at the bedside
  – Even more difficult when reading about the reaction on paper
TRALI Risk Mitigation Strategies: 2º Prevention

- Cases of potential TRALI are summarised and voted on independently by members of the TMRG
- Donor investigation and management depends on TMRG final assessment – group discussion
- Hospital decides final categorization of adverse event for TTISS or other reports

<table>
<thead>
<tr>
<th>TRALI</th>
<th>Possible TRALI</th>
<th>TRALI Inconclusive</th>
<th>TACO</th>
<th>TAD</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCC</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>final</td>
<td></td>
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</tbody>
</table>
TRALI Medical Working Group (TMRG)

- 2000 – a group of CBS medical directors developed a protocol for TRALI reaction investigation and set up a database and testing with $15,000 grant

- January 2001 started collecting data and testing samples (SMH – Dr. John Freedman’s lab)

- Used CCC criteria

- 2006 – adverse event investigation including TRALI was formalized in an SOP and the TMRG was formed

- 2008 testing transferred to Winnipeg
It is important to note that the hospital and CBS have different perspectives:

Hospital
- Manages the patient
- TRALI is a clinical diagnosis (often complex multifactorial patient confounders)
- No diagnostic test available

CBS
- Reviews case as submitted by hospital
- Follows CCC criteria
- Want to be sure it is the transfusion and not “other”
- Donor management – is the donor unsafe for recipients
TMRG meets approximately monthly

Current members:
- Lynnette Beaudin
- Gwen Clarke
- Judy Hannon
- Mary Huang
- Debra Lane
- Chantale Pambrun
- Tanya Petraszko
- Kathryn Webert
- Dale Young
- Michelle Zeller

Past members:
- Ines Bonacossa
- Barbara Hannach
- Heather Hume
- Yulia Lin
- Chee Loong Saw
Cases submitted by hospital, summarized by TMRG member for group to confidentially “vote” prior to meeting (“just the facts”…)

Often robust discussion at the meeting

Err on the side of caution

Canadian Concensus Conference criteria followed

(*additional category – “TRALI inconclusive” - ..)

Once a donor is implicated in a TRALI reaction, even if current (HLA) testing is negative – donor can only donate RP

In practical terms we rarely see these donors again.

Letter of decision sent to the CBS Medical Officer (and then on to the hospital) on behalf of the TMRG.

If donor investigation is undertaken a letter of conclusion is again sent to the CBS MO (and then to hospital) – if donors don’t provide samples by 1 year the case is closed. (although can be re-opened if donor subsequently presents)
After TMRG Review

TRALI and Canadian Blood Services

Chart shows data from 2006 to 2014, with categories for Other, TACO/TAD, Incon, and Def/pos. Slide modified from Mary Huang.
TRALI Risk Mitigation Strategies: 2° Prevention

- If TRALI (including possible, inconclusive):
  - Donor coded (unable to donate until testing completed)
  - Required to provide samples for testing
  - Sent a letter requesting that the attend a clinic to provide samples for testing
  - Mailed results and future eligibility when available (approximately 4 to 6 weeks)
TRALI Risk Mitigation Strategies: 2° Prevention

• If determined to not be TRALI:
  – Donor coded with surveillance code
    – *If associated with any adverse reaction in future, will be assessed for future eligibility*
  – No testing done on the donor
  – Can continue to donate all components
Status of testing for TRALI at Canadian Blood Services
TRALI Laboratory Testing

• HLA Class I and II antibody screening and specificity determination using cytometric microbead assay with Luminex technology (One Lambda Inc)

• Recipient HLA molecular typing done by Luminex (if sample available)

• No neutrophil testing performed
  – One Lambda kit that is currently licensed in Canada tests only for HNA 1A, 1B, 1C, 2 (does not test for HNA-3, 4 and 5)

• Recipient-donor crossmatch not done
TRALI Laboratory Testing

- Positive anti-HLA antibody
  - Defer

- Negative anti-HLA antibody
  - Can only collect recovered plasma, washed red cells (if rare donor)
  - Can not re-instate donor as testing for HNA antibodies has not been performed
TRALI: Incidence

Number of Adverse Reactions

<table>
<thead>
<tr>
<th>Year</th>
<th>Total ARs</th>
<th>Suspected TRALI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>140</td>
<td>57</td>
</tr>
<tr>
<td>2008</td>
<td>123</td>
<td>35</td>
</tr>
<tr>
<td>2009</td>
<td>111</td>
<td>35</td>
</tr>
<tr>
<td>2010</td>
<td>118</td>
<td>39</td>
</tr>
<tr>
<td>2011</td>
<td>103</td>
<td>38</td>
</tr>
<tr>
<td>2012</td>
<td>72</td>
<td>34</td>
</tr>
<tr>
<td>2013</td>
<td>43</td>
<td>27</td>
</tr>
<tr>
<td>2014</td>
<td>38</td>
<td>12</td>
</tr>
<tr>
<td>2015</td>
<td>36</td>
<td>22</td>
</tr>
<tr>
<td>2016</td>
<td>55</td>
<td>24</td>
</tr>
</tbody>
</table>

Canadian Blood Services
it's in you to give
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>57</td>
<td>35</td>
<td>35</td>
<td>39</td>
<td>38</td>
<td>33</td>
<td>27</td>
<td>12</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>Male plasma (Oct 2007)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Male plasma (Jan 2008)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite and Possible</td>
<td>36</td>
<td>20</td>
<td>12</td>
<td>10</td>
<td>8</td>
<td>14</td>
<td>7</td>
<td>5</td>
<td>2</td>
<td>9</td>
</tr>
</tbody>
</table>

Male plasma (Oct 2007) and Male plasma (Jan 2008)
Number of TRALI cases

- Total: 57, 35, 35, 39, 38, 34, 27, 12, 22, 24
- Central Ontario: 38, 13, 18, 24, 22, 20, 7, 5, 10, 6

PMP for transfusion and suspension of BCPM October 2007
BCPM in Central Ontario January 2008
<table>
<thead>
<tr>
<th>Component</th>
<th>2008-2016</th>
<th>Gender</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red Cells</td>
<td>53 cases</td>
<td>Male only</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female only</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Both</td>
<td>7</td>
</tr>
<tr>
<td>Plasma</td>
<td>6 cases</td>
<td>Male only</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Both</td>
<td>2</td>
</tr>
<tr>
<td>Platelets</td>
<td>13 cases</td>
<td>Male only</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Both</td>
<td>8</td>
</tr>
<tr>
<td>Mixed</td>
<td>15 cases</td>
<td>Male only</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Both</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>87 cases</td>
<td>Male only</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female only</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Both</td>
<td>26</td>
</tr>
</tbody>
</table>
# Components with Cognate Antibody

## Definite and Possible TRALI 2008 to 2016

<table>
<thead>
<tr>
<th>Component</th>
<th>Gender</th>
<th>Cognate</th>
<th>Component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red Cells</td>
<td>Male</td>
<td>2</td>
<td>AS-3 (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B2 (1)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>8</td>
<td>AS-3 (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B1 (5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B2 (2)</td>
</tr>
<tr>
<td>Plasma</td>
<td>Male</td>
<td>4</td>
<td>FP (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AFFP (1)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>2</td>
<td>AFFP (2)</td>
</tr>
<tr>
<td>Platelets</td>
<td>Male</td>
<td>3</td>
<td>BC Plts (3)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>6</td>
<td>BC plts (6)</td>
</tr>
<tr>
<td></td>
<td>RBC</td>
<td>plasma</td>
<td>plt</td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>2012</td>
<td>23(67%)</td>
<td>0(0%)</td>
<td>4(12%)</td>
</tr>
<tr>
<td>2013</td>
<td>18(67%)</td>
<td>2(7%)</td>
<td>3(11%)</td>
</tr>
<tr>
<td>2014</td>
<td>7(58%)</td>
<td>1(8%)</td>
<td>2(17%)</td>
</tr>
<tr>
<td>2015</td>
<td>11(50%)</td>
<td>1(4%)</td>
<td>5(23%)</td>
</tr>
<tr>
<td>2016</td>
<td>14(58%)</td>
<td>2(8%)</td>
<td>4(17%)</td>
</tr>
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</table>
### Gender of donors associated with TRALI

<table>
<thead>
<tr>
<th>Year</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>51 (59%)</td>
<td>36 (41%)</td>
<td>87</td>
</tr>
<tr>
<td>2013</td>
<td>72 (68%)</td>
<td>34 (32%)</td>
<td>106</td>
</tr>
<tr>
<td>2014</td>
<td>33 (61%)</td>
<td>21 (39%)</td>
<td>54</td>
</tr>
<tr>
<td>2015</td>
<td>71 (66%)</td>
<td>36 (34%)</td>
<td>107</td>
</tr>
<tr>
<td>2016</td>
<td>57 (67%)</td>
<td>28 (33%)</td>
<td>85</td>
</tr>
</tbody>
</table>

![Graph showing gender distribution over years](image-url)
National Consolidation of the HLA/HPA Matched Platelet Process

“Making the HLA - Matched Platelet Programme GREAT AGAIN”
Managing requests for HLA matched platelets is performed in an ad-hoc way in 12 separate sites within Canadian Blood Services.

There is variation in the way processes are executed within CBS and, more critically, variation in our outward facing response to customer needs.

There is opportunity to significantly improve patient care by focusing our efforts on improving the management of HLA platelet requests including:

- Donor recruitment and follow-up
- Collection, production
- Inventory management and distribution
- Efficacy
A few “facts”

Number of HLA matched donors in our registry: 12,500 (20,000 optimal?)

Number of plateletpheresis products collected annually: 40,559 in 2016

Percentage plateletpheresis products collected that are LVP – about 80%

Percentage of plateletpheresis products that are HLA matched and issued for a particular patient: 5% (?)

Percentage of HLA matched requests that are filled with an appropriately matched product - UNKNOWN
The project intends to standardize processes and consolidate management and oversight of a national HLA Matched Platelet Program

Overall the outcome goals of this consolidation project are to:

- Ensure that the number of HLA/HPA typed plateletpheresis donors is adequate to meet patient needs
- Increase the number and diversity of the donors if required
- Ensure that ordering practices for this specialized product meet appropriate indications
- Develop standardized algorithms for donor selection depending on degree of match (e.g. 4/4 vs 1/4 vs least incompatible)
- Develop a mechanism to track and report the number of matches, including degree of compatibility match
- In hospitals where collaboration is feasible, implement post transfusion patient monitoring protocols to monitor product effectiveness
This initiative is part of the grouping of initiatives that make up the larger Platelet Program for Canadian Blood Services and supports the specialized products and services included in the Rare Blood Program.

The consolidation will be rolled out in two parts:

Phase 1 – implement in Medical Services West (BC, AB, SK, and MB)

Phase 2 – implement in Medical Services East (ON, and Atlantic regions)
Advantages of defining, standardizing, and consolidating the national process include:

1) This gives CBS an opportunity to provide a consistent national approach to HLA/HPA matched platelet collections and distribution

2) This allows CBS to track product efficacy and refine donor selection for individual recipient needs

3) In the event of a service interruption at one of the Medical Services regional offices, the other office can function as backup
There is a lot of “behind the scenes” planning involving many departments within CBS

Medical Offices – including physicians, RN’s, and support staff
Platelet Immunology Lab in Winnipeg
Production and Distribution
Donor Testing
Donor Relations  (Collections and Recruitment including our National Contact Centre)
IT and Records Management
Transportation/Logistics
Privacy
Quality Assurance
But what does this mean to our hospitals?

Urgent/Emergent requests for these products (most commonly HPA) are sporadic, and these processes will remain unchanged in the way the hospital requests them and in the way the CBS Distribution staff manages them.

Non-urgent HLA matched platelet requests will continue to be requested in much the same way as you are now – through the Distribution staff that you regularly communicate with. `(patient diagnosis, patient platelet count, HLA typing and HLA antibodies, patient sample testing if requested, repeat HLA antibody screen at intervals, and anticipated frequency and duration of support)`
Internally, our consolidated process will be initiated through communication from our Distribution staff and should be seamless to you.

We will, however be:

1) Reviewing requests for this specialized product to ensure appropriate indications for use are met.

2) Requesting pre & post transfusion platelet counts to be performed and communicated to us, thereby assisting us in ongoing donor selection.

3) Communicating closely with you to ensure that we aren’t booking donors when the product is no longer required.
Acknowledgements:

Mary Huang
Kathryn Webert
TMRG members
Questions?