Transfusion-transmitted Cytomegalovirus

Can you confidently abandon CMV seronegative products in the modern era of pre-storage leukoreduction?

Jeannie Callum, BA, MD, FRCPC
Really?

Are we still talking about this in 2017?
Disclosure

• I am not:
  – A virologist
  – A microbiologist
  – An expert researcher on transfusion-transmitted cytomegalovirus

• I am:
  – A reasonable person
  – An early adopter of leukoreduction as a sole strategy for CMV prevention

• No “official disclosures”
Sunnybrook, UHN & Partners

- Neonates: in 2001 we (in conjunction with Hospital for Sick Kids) stopped dual coverage (breast milk contamination studies)
- Rest of high risk populations:
  - Complete abandonment at Sunnybrook: 2012
  - [Note: Ottawa abandoned for HSCT in 2009]
  - Complete abandonment at 27 sites: 2015
- We have HSCT, solid organ transplants, pregnant women, HIV patients, neonates
- The only thing we don’t do is intrauterine transfusions
Outline

• Biology & epidemiology of CMV
• History of transfusion-transmitted CMV
• Blood donor CMV science
• Modern day leukoreduction failure rates
• Systematic review from AABB CTMC
• Larger clinical reports – HSCT, SOT, neonates
• When you need to test HSCT and SOT patients
• Review the National Advisory Committee Recommendation
• Conclusion
Basic Biology of CMV

- CMV or HHV-5 is a herpes virus
- Infected via mucosal epithelial cells
  - Vertical, breast milk, sexual contact (any), transfusion, HSCT, solid organ transplant, iv drugs
- Remains latent in myeloid cells for life
- Primary infection and the risk of reactivation (usually during illness including postpartum)
  - 4-8 week from infection to CMV Ab
  - DNA+ > IgM > IgG
- Seropositive: women, older patients, lower economic status, MSM
- About 40% of Canadians are seropositive (much lower than most other countries)
- 1% annual seroconversion rate in healthy blood donors
Epidemiology of CMV

- Vertical/breast milk
- Mother-child salivary contact
- Sexual contact

Blood transfusion
History of TT-CMV prevention

Warm whole blood 1 in 2

Refrigerated whole blood 1 in 100

Seronegative non-LR 1 in 66,000

Pre-storage LR only 1 in 13,575,000

Seed et al. Vox Sang 2015; 109: 11-17
Allain et al. Biologicals 2009; 37: 71-77
If the risk is 1 in 13 million why am I speaking about this today?

I think because blood bankers are neurotic about accepting any possible risk
Compared to other viruses

<table>
<thead>
<tr>
<th>Virus</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>1 in 21 million</td>
</tr>
<tr>
<td>CMV</td>
<td>1 in 13.5 million*</td>
</tr>
<tr>
<td>HCV</td>
<td>1 in 13 million</td>
</tr>
<tr>
<td>HBV</td>
<td>1 in 7.5 million</td>
</tr>
</tbody>
</table>

* But remember half of recipients already infected!
### Compared to other viruses

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CMV Donor Science

• CMV-neg units can transmit CMV because the window period after infection until Ab positive is 4-8 weeks
  – Unknown how long the infectious window is (some donors may self defer “don’t feel well”)
  – LR may not help as 0.13% have detectable CMV DNA
  – Unclear how efficient cell free CMV DNA is at transmission
• LR units can transmit CMV because of the incomplete removal of white blood cells in rare units due to failure
  – I could not find a single case report of confirmed transfusion transmission from pre-storage LR only
• Some experts recommend the safest CMV product would be from selection of CMV seropositive donors at least 1 year after seroconversion
  – You also get “passive immunity” from donor IgG

Ziemann et al. Transfusion 2007; 47: 1972-83
Zanghellini et al. J Infect Dis 1999; 180: 702-7
CMV DNA in recent seroconverters

![Bar graph showing CMV DNA positivity across different intervals since last seronegative donation (days). The graph indicates a significant increase in positivity for intervals less than 120 days compared to 120 to 729 days and 730 or more days.](image)

# CMV DNA in different donors

<table>
<thead>
<tr>
<th>Donor status</th>
<th>N</th>
<th>CMV DNA+</th>
<th>CMV DNA-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seronegative</td>
<td>150</td>
<td>0</td>
<td>150</td>
</tr>
<tr>
<td>Seropositive &gt;1 yr</td>
<td>450</td>
<td>0</td>
<td>450</td>
</tr>
<tr>
<td>Sero “negative”</td>
<td>68</td>
<td>2</td>
<td>64</td>
</tr>
<tr>
<td>New SP “first”</td>
<td>82</td>
<td>36</td>
<td>43</td>
</tr>
<tr>
<td>New SP “second”</td>
<td>71</td>
<td>4</td>
<td>66</td>
</tr>
</tbody>
</table>

62% of SC are DNA+
CMV positive donors

- 2 studies including 1,086 CMV+ donors
- No DNA+ donations in follow-up
  

- 1 study including 7,303 CMV+ donors
- 1 DNA donations in follow-up – low IgG and very low CMV DNA (<30 IU/mL)
  

- Led to the common recommendation that CMV+ donors >1 year out = lowest risk donor
  
Many CMV-neg donors are DNA+

- 41% of CMV+ donors have CMV DNA in their WBCs
  - If you enrich the sample with monocytes then 71% CMV DNA+
- 13% of CMV- donors have CMV DNA in their WBC
  - If you enrich the sample with monocytes then 55% CMV DNA+

TRANSFUSION 1998;38:271-278.
# Pre-storage LR in 2015

<table>
<thead>
<tr>
<th>Variable</th>
<th>B1 RBC</th>
<th>B2 RBC</th>
<th>BC-platelet</th>
<th>A-platelet</th>
</tr>
</thead>
<tbody>
<tr>
<td># tested</td>
<td>5045</td>
<td>3401</td>
<td>1210</td>
<td>1116</td>
</tr>
<tr>
<td>WBC median</td>
<td>0.063 x 10^6</td>
<td>0.080 x 10^6</td>
<td>0 x 10^6</td>
<td>0 x 10^6</td>
</tr>
<tr>
<td>Pass rate</td>
<td>99.88%</td>
<td>99.76%</td>
<td>100.00%</td>
<td>100.00%</td>
</tr>
</tbody>
</table>

FDA recommendation = <5 x 10^6  
Other countries = <1 x 10^6

CBS, personal communication
Systematic Review of Clinical Studies

• 11 studies (7 observational with 949 pts; 4 RCTs with 680 pts)
• 7 chemo/HSCT; 4 infants
• Only 3 studies “modern” with pre-storage leukoreduction (677 pts; 2002/2003/2013)
• Infant studies problematic as infants fed CMV+ infected breast milk included
• No attempt to link donor to recipient
• Only 2 looked at LR vs. LR plus seronegative

Mainou et al. Transfusion 2016; 29 January 2016
Systematic Review

### CLINICAL CMV INFECTION

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Treatment</th>
<th>Control</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kekre 2013 (HSCT)</td>
<td>4.33 (0.21, 88.90)</td>
<td>2/89</td>
<td>0/77</td>
<td>100.00</td>
</tr>
<tr>
<td>Ljungman 2002 (HSCT)</td>
<td>(Excluded)</td>
<td>0/33</td>
<td>0/49</td>
<td>0.00</td>
</tr>
<tr>
<td>Subtotal</td>
<td>4.33 (0.21, 88.90)</td>
<td>2/122</td>
<td>0/126</td>
<td>100.00</td>
</tr>
</tbody>
</table>

### LABORATORY CMV INFECTION

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Treatment</th>
<th>Control</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kekre 2013 (HSCT)</td>
<td>2.60 (0.28, 24.44)</td>
<td>3/89</td>
<td>1/77</td>
<td>25.55</td>
</tr>
<tr>
<td>Ljungman 2002 (HSCT)</td>
<td>0.74 (0.20, 2.76)</td>
<td>3/33</td>
<td>6/49</td>
<td>74.45</td>
</tr>
<tr>
<td>Subtotal</td>
<td>1.02 (0.33, 3.18)</td>
<td>6/122</td>
<td>7/126</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis
Thiele – Germany HSCT

• 23 CMV -/- HSCT patients
• 3180 donor exposures of pre-storage LD only
• No seroconversions
• 17 of 23 had passive IgG detected (IgM neg, DNA neg)

Nash – Michigan HSCT

- 100 CMV -/- HSCT patients
- Followed weekly for CMV DNA
- Transfused 3690 units of LR-only
- No seroconversions
- 2/100 transient IgG CMV Ab positive (IgM neg, DNA neg) due to passive Ab

Kekre - Ottawa HSCT

89 LR and CMV-
77 LR only

Just -/- transplants

4 CMV PCR+
- 3 LR and CMV-
- 1 LR only

2 CMV disease
- Both LR and CMV-

Figure 3. Overall survival by transfusion group.
Hall – Oxford/Birmingham HSCT

• 76 CMV -/- HSCT patients
• Followed weekly for CMV DNA
• Transfused 1862 donor exposures of LR-only
• No seroconversions

Solid organ transplant

- Non-LR, CMV untested; details fuzzy

<table>
<thead>
<tr>
<th>Type of allograft</th>
<th>CMV serostatus of recipient and donor</th>
<th>Number of CMV patients infected* (%)</th>
<th>Number of patients who were transfused (%)</th>
<th>Number of R–D– patients who developed CMV/number transfused (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>R–D–</td>
<td>0/71 (0%)</td>
<td>57/71 (80.3%)</td>
<td>0/57 (0%)</td>
</tr>
<tr>
<td></td>
<td>R–D+</td>
<td>69/81 (85.2%)</td>
<td>62/81 (76.5%)</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>R–D–</td>
<td>0/29 (0%)</td>
<td>29/29 (100%)</td>
<td>0/29 (0%)</td>
</tr>
<tr>
<td></td>
<td>R–D+</td>
<td>28/32 (87.5%)</td>
<td>32/32 (100%)</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>R–D–</td>
<td>1/7 (14.3%)</td>
<td>6/7 (85.7%)</td>
<td>1/6 (16.7%)</td>
</tr>
<tr>
<td></td>
<td>R–D+</td>
<td>9/10 (90.0%)</td>
<td>10/10 (100%)</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>R–D–</td>
<td>2/20 (10.0%)</td>
<td>20/20 (100%)</td>
<td>2/20 (10.0%)</td>
</tr>
<tr>
<td></td>
<td>R–D+</td>
<td>25/31 (80.6%)</td>
<td>31/31 (100%)</td>
<td></td>
</tr>
</tbody>
</table>
Premature neonates

- 462 mother and 539 LBW infant “pairs”
- 76.2% of mothers were CMV antibody positive
- CMV infection rate among infants was 7% at 12 weeks
- A total of 2061 CMV-seronegative and LR transfusions administered
  - No cases of transfusion-transmitted CMV
- 96% of cases were from breast milk (1 other route)
- What is the point of CMV seronegative and leukoreduced if breast milk feeds are continued?

Why can’t clinical trials answer this question?

<table>
<thead>
<tr>
<th>Product</th>
<th>Probability</th>
<th>95% confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC</td>
<td>1 in 7,790,000</td>
<td>1 in 771,307,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 in 993,000</td>
</tr>
<tr>
<td>Platelets</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 in 1,074,000</td>
</tr>
<tr>
<td>Combined</td>
<td>1 in 13,575,000</td>
<td>1 in 1,344,167,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 in 1,730,000</td>
</tr>
</tbody>
</table>

RBC unit $[p(Inf)] = p(f) \times p(viraemia)$

$= 0.001083 \times 0.0011850538$

$= 1.2837 \times 10^{-7}$ (95% CI:

$1.297 \times 10^{-9} - 1.007 \times 10^{-6}$) or,

1 in 7789519 (95% CI:

1 in 771306874 – 1 in 992979).

Seed et al, Vox Sang 2015; 109: 11-17
Criticism of Seed et al.

• They excluded infections from cell free DNA…but the authors argued:
  – Theoretical only
  – No reported cases of CMV transmission by FFP
  – Cell free DNA is highly fragmented
  – Studies in mice fail to demonstrate any infectivity
Logistical issue

• You **MUST** draw CMV Ab testing for potential HSCT and SOT patients before their 1\textsuperscript{st} platelet transfusion!

• Observational study of 31 HSCT patients
  – 35.5% did not have their CMV Ab checked before 1\textsuperscript{st} transfusion
  – 93.5% had multiple CMV Ab tests pre-transplant
  – 27.6% had “flipping” results suggesting passive Ab detection
  – 1 CMV-neg donor had a CMV-pos donor selected in error

## Overall conclusion

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Recommendation</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>LD only</td>
<td>74% of CMV+ mother have CMV in breast milk</td>
</tr>
<tr>
<td>Solid organ</td>
<td>LD only</td>
<td>CMV transmission from “LR only” never detected in</td>
</tr>
<tr>
<td>HSCT (allogeneic)</td>
<td>LD only</td>
<td>CMV transmission from “LR only” rare unproven cases in</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>LD only</td>
<td>40% seropositive and 3.9% seroconversion rate in pregnancy¹</td>
</tr>
<tr>
<td>HIV</td>
<td>LD only</td>
<td>High baseline rates of CMV infection (&gt;90%)</td>
</tr>
<tr>
<td>Intrauterine</td>
<td>CMV+&gt;1 year CMV DNA-</td>
<td>Highly unlikely that the CMV DNA step adds additional safety…but perhaps after a large HSCT cohort study we can abandon this</td>
</tr>
</tbody>
</table>

* Must do CMV Ab testing before 1st platelet transfusion or IVIG administration

1. Lamarre et al. Epidemiolog Infect 2015; epub ahead of print
Cost to Canadian Blood Services?

$700,000
(just the testing kit cost)

Personal communication, CBS, 2012
Just a guess

We are probably spending $1-2 million on CMV seronegative testing and distribution (add labour, transportation, transfusion delays)
Platelets

% CMV Neg Platelet Orders of Total Platelet Orders

<table>
<thead>
<tr>
<th>Year</th>
<th>CMV Neg %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009/10</td>
<td>35.0%</td>
</tr>
<tr>
<td>2010/11</td>
<td>34.8%</td>
</tr>
<tr>
<td>2011/12</td>
<td>34.1%</td>
</tr>
<tr>
<td>2012/13</td>
<td>32.9%</td>
</tr>
<tr>
<td>2013/14</td>
<td>29.2%</td>
</tr>
<tr>
<td>2014/15</td>
<td>26.9%</td>
</tr>
<tr>
<td>2015/16</td>
<td>23.1%</td>
</tr>
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</table>
Variability by Province

% CMV Neg Platelet Orders of Total Platelet Orders by Province

PEI: 2013/14: 4.0%, 2014/15: 37.9%, 2015/16: 58.4%
ONT: 2013/14: 16.3%, 2014/15: 44.0%, 2015/16: 62.9%
ALB: 2013/14: 13.4%, 2014/15: 35.5%, 2015/16: 26.0%
National Advisory Committee Recommendations on CMV Prevention

• NAC recommends that CMV safe (LR) and CMV IgG seronegative products be considered equivalent except for Intrauterine transfusion

• NAC recommends that CBS stop their current process for testing and provision of CMV seronegative units issued to hospital facilities and develop a new process to maintain a small inventory of CMV seronegative blood components for the sole purpose of Intrauterine transfusion (IUT)

• NAC recommends that CBS explores the feasibility of providing a small boutique inventory of dually tested (seronegative and NAT) CMV negative blood components for the sole purpose of IUT

http://www.nacblood.ca/resources/guidelines/CMV.html
Summary

• CMV is present in half the population and transfusion (if ever) is NOT a common route of infection
• History of transfusion-transmitted CMV
  – We have decreased the risk from 1 in 2 to about 1 in 13 million
• Blood donor CMV science
  – Evidence suggests long-term CMV+ donors may be the safest
• Modern day leukoreduction failure rates
  – Never for platelets and rare for RBCs
• CMV seronegative and leukoreduction are NOT additive in terms of protection
• Test HSCT and SOT patients before the first platelet transfusion to avoid passive Ab issue
• No proven cases of CMV transmission from LR-only in HSCT or other recipients
If the risk of TT-CMV is 1 in 13.5 million we will never have RCTs... so...STOP WAITING FOR THEM