Optimal / Evidence-based Method to Prevent Transmission of Cytomegalovirus (CMV) by Transfusion

Presenter
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Associate Medical Director, LifeSource/ITxM
Terms

• “CMV Negative” means the donor is CMV antibody negative (CMV Seronegative)
• “CMV Safe” means leukocyte-reduction by the blood supplier (usually pre-storage filtration or apheresis technology)
Evidence-based Bottom Line: Preview

- Most effective overall (ie, efficacy, convenience, cost) way to prevent transfusion-transmitted CMV is consistent leukocyte-reduction (<5x10^6/unit)
- “belt & suspenders” combination of leukocyte-reduction of CMV Antibody/seronegative units not superior efficacy; actually inferior in convenience & cost.
- CMV Antibody/seronegative alone, washing, frozen/thawed archaic, inconsistent, inconvenient, costly.
- Pathogen reduction efficacious, but emerging.
INTERCEPT Achieves >4 logs of Inactivation for Most Pathogens Tested meeting FDA standards for pathogen reduction.

<table>
<thead>
<tr>
<th>Viruses</th>
<th>Log Reduction (pfu/mL)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1, cell-associated</td>
<td>≥5.4</td>
</tr>
<tr>
<td>DHBV (model virus for HBV)</td>
<td>≥4.8</td>
</tr>
<tr>
<td>BVDV (model virus for HCV)</td>
<td>≥4.4</td>
</tr>
<tr>
<td>HTLV-I</td>
<td>4.7</td>
</tr>
<tr>
<td>HTLV-II</td>
<td>≥5.1</td>
</tr>
<tr>
<td>West Nile Virus</td>
<td>≥5.7</td>
</tr>
<tr>
<td>Chikungunya virus (CHIKV)</td>
<td>≥5.7</td>
</tr>
<tr>
<td>Dengue virus (DENV)</td>
<td>≥4.3</td>
</tr>
<tr>
<td>Cytomegalovirus (CMV), cell-associated</td>
<td>≥4.9</td>
</tr>
<tr>
<td>Influenza A virus</td>
<td>≥5.9</td>
</tr>
<tr>
<td>Bluetongue virus</td>
<td>4.4</td>
</tr>
<tr>
<td>Adenovirus 5</td>
<td>≥4.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Protozoan Parasites</th>
<th>Log Reduction (pfu or cfu/mL)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasmodium falciparum (malaria)</td>
<td>≥5.6</td>
</tr>
<tr>
<td>Babesia microti</td>
<td>≥4.9</td>
</tr>
<tr>
<td>Trypanosoma cruzi (Chagas)</td>
<td>≥5.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Log Reduction (cfu/mL)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia coli</td>
<td>≥6.3</td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
<td>≥5.9</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>5.8</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>≥6.7 ²</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>≥6.1</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>≥5.4</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>≥6.8 ²</td>
</tr>
<tr>
<td>Bacillus cereus (vegetative)</td>
<td>≥5.5</td>
</tr>
<tr>
<td>Bacillus cereus (spore forming)</td>
<td>3.7 ²</td>
</tr>
<tr>
<td>Clostridium perfringens (vegetative)</td>
<td>≥6.5</td>
</tr>
<tr>
<td>Propionibacterium acnes</td>
<td>≥6.5</td>
</tr>
<tr>
<td>Treponema pallidum (syphilis)</td>
<td>≥6.4</td>
</tr>
<tr>
<td>Borrelia burgdorferi (lyme disease)</td>
<td>≥6.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Leukocytes</th>
<th>Log Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human T-Cells</td>
<td>4.0</td>
</tr>
</tbody>
</table>

¹Based on input titer and post-treatment titer in 1 mL. For a full list of pathogens, see Package Insert.
²Based on culture of full platelet unit (300 mL).
Biology of and testing for Human Cytomegalovirus (HCMV)

(with permission: Sanobar Khan, MD. FACP)
HCMV
HCMV

- CMV is a double stranded DNA virus
- Herpesvirus family
- CMV infection is world wide
- Antibody prevalence in adults range from 20-80%
- HCMV has the largest genome of all herpes viruses
- Genome encodes at least 80 proteins
- Patient may be re-infected by the same genotype or by a different genotype (only rarely documented)
- Cells such as respiratory tract epithelium and leukocytes support primary infection, while latent infection is established in Lymphocytes.
<table>
<thead>
<tr>
<th>Name</th>
<th>Target cell type</th>
<th>Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV1</td>
<td>Mucoepithelia</td>
<td>Neuron</td>
</tr>
<tr>
<td>HSV2</td>
<td>Mucoepithelia</td>
<td>Neuron</td>
</tr>
<tr>
<td>VSV</td>
<td>Mucoepithelia</td>
<td>Neuron</td>
</tr>
<tr>
<td>EBV</td>
<td>B-lymphocytes</td>
<td>B-lymphocytes</td>
</tr>
<tr>
<td>CMV</td>
<td>Monocytes/lymphocytes</td>
<td>Leukocytes</td>
</tr>
<tr>
<td>HHV6</td>
<td>Leukocytes</td>
<td></td>
</tr>
<tr>
<td>HHV7</td>
<td>Leukocytes, kidney</td>
<td></td>
</tr>
<tr>
<td>HHV8</td>
<td>T and B lymphocytes</td>
<td></td>
</tr>
</tbody>
</table>
HCMV

• **Latent infection**: Human cytomegalovirus (HCMV) persists as a sub-clinical, lifelong infection in the human host which is maintained at least in part by its carriage in the absence of detectable infectious virus.

• **Reactivation**: In contrast, reactivation from latency in immuno-compromised individuals can result in serious disease.

• **Seroconversion**: Detectable specific antibody as a result of infection/immunization.

• **Seroprevalence**: Number of persons in a population who test positive for a specific disease based on serology.
HCMV

- CMV primary infection
- CMV seroconversion in healthy blood donors
  0.6-3.3%
- CMV seroprevalence 20-80% (highest lower socioeconomic, inner city, IV drug abuse, sexual promiscuity)
Lab Diagnosis

• Virus Isolation:
  – Cell culture
  – DEAFF: Detection of early antigen fluorescent foci
  – Histopathology
  – Tissue immunofluorescence
  – EM
  – Elisa Test: latex agglutination for Blood products
  – CMV DNA by PCR
  – CMV antigenemia test
Lab Diagnosis (continued)

- Serology:
  - IgM: detected in primary infection
  - IgG: long-term immune status
CMV Safe vs CMV Antibody Negative

Blood products to prevent transfusion transmitted CMV are leukocyte-reduced, CMV sero/antibody negative, or both (‘belt & suspenders’)

Background

- For reasons one can only speculate about, but are undoubtedly multiple and interactive, symptomatic transfusion-transmitted CMV is extremely uncommon.
- Selecting blood/blood components using ONLY leukocyte-reduction done by the blood supplier (ie, NOT bedside) has been shown by many to effectively prevent/reduce transfusion-transmitted CMV. There are no data documenting superiority of blood from CMV antibody negative donors --- even when combined with leukocyte-reduction.
Caveats of Historic L-R & CMV Studies

- Only 6 of 15 studies controlled
- L-R accomplished by several techniques
- CMV occurred 15% (33/220) if no protection
  CMV occurred 0.8% (2/249) with seroneg
  CMV occurred 0.96% (7/731) with L-R
  (3 of 7 not likely due to transfusion)
## L-R Reduces Transfusion-Transmitted CMV

<table>
<thead>
<tr>
<th>Author</th>
<th>L-R (CMV/subjects)</th>
<th>No L-R (CMV/subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowden</td>
<td>0/17   filter</td>
<td>7/30</td>
</tr>
<tr>
<td>Bowden</td>
<td>0/37   &quot;</td>
<td>___</td>
</tr>
<tr>
<td>Bowden</td>
<td>3/247  &quot; (bedside)</td>
<td>2/249 (seroneg)</td>
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<tr>
<td>Verdonck</td>
<td>0/29   &quot;</td>
<td>___</td>
</tr>
<tr>
<td>Van Prooijen</td>
<td>0/60   &quot;</td>
<td>___</td>
</tr>
<tr>
<td>Bacigalupo</td>
<td>0/17   &quot;</td>
<td>___</td>
</tr>
<tr>
<td>Andreu</td>
<td>0/8    &quot;</td>
<td>___</td>
</tr>
<tr>
<td>Gilbert</td>
<td>0/30   &quot;</td>
<td>9/42</td>
</tr>
<tr>
<td>Pamphilon</td>
<td>0/62   &quot;</td>
<td>___</td>
</tr>
<tr>
<td>Narvios</td>
<td>1/45   &quot;</td>
<td>___</td>
</tr>
<tr>
<td>Ohto</td>
<td>3/33   &quot; (milk)</td>
<td>1/19</td>
</tr>
<tr>
<td>Graan-Hentzen</td>
<td>0/59   filter, centrif</td>
<td>10/86</td>
</tr>
<tr>
<td>de Witte</td>
<td>0/37   &quot; , &quot;</td>
<td>___</td>
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<tr>
<td>Murphy</td>
<td>0/11   &quot; , &quot;</td>
<td>6/43</td>
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<tr>
<td>Eisenfeld</td>
<td>0/48   filter, SCF</td>
<td>___</td>
</tr>
</tbody>
</table>
Modern Studies Transfusion-Transmitted CMV

- Randomized trial leukocyte-reduction vs CMV Antibody seronegative units vs both “belt & suspenders” impossible
- Decisions per sequential cohort observational studies
- Leukocyte-reduction alone eliminates transfusion CMV
  Nash et al. Transfusion 2012; 52: 2270
  Thicle et al. Transfusion 2011; 51: 2620
- “Belt & suspenders” eliminates transfusion CMV
  Josephson et al. Jama Pediatric 2014; 168: 1054
Belt & Suspenders Approach

- I agree with many, many, many others throughout the World that the best CMV-safe blood is that which is leukocyte-reduced by the blood supplier --- without regard for the CMV antibody status of donor/unit.
- The "belt-&-suspenders" approach, although appealing and popular, is problematic because it has NOT been shown to be superior.
- It is more expensive, and sometimes compromises availability, which may lead to delays while searching for CMV antibody negative units to, then, leukocyte-reduce.
References

6) Thiele. Transfusion 2011; 51: 2620.