Preventing CMV Transmission through Leukodepletion

Possibility & Facts

Prof. S. B. Rajadhyaksha, MD, DTM, PGDMLS
Head, Dept. of Transfusion Medicine
Tata Memorial Hospital, Mumbai
Donor Leukocytes

- Linked to a wide range of complications in transfusion recipients

- Acute and long-term complications can result directly from exposure to donor leukocytes
ADVERSE EFFECTS OF CONTAMINATING LEUCOCYTES

- HLA Alloimmunisation
  - Platelet Refractoriness
  - Graft Rejection

- Viral Transmission
  - CMV
  - EBV
  - HTLV-I
  - HIV reactivation

- Immune Suppression
  - Post operative infections
  - Cancer Recurrence

Reactions
- NHFTR
- GVHD

Contaminating Leucocytes
Cytomegalovirus (CMV)

CMV - largest human herpes virus
resides exclusively in WBC

Epidemiology

- North America - 30% to 80% CMV antibody
- India - 95% CMV IgG antibody
- Incidence of infection is 1-4% even with seronegative blood
- After either kidney or liver transplants, more than 60% of patients develop antibodies against CMV
Cytomegalovirus (CMV)

- A virus belonging to the herpes group that is rarely transmitted by blood transfusion.
- According to the Centers for Disease Control and Prevention (CDC), about 50 to 85 percent of adults in the United States are infected with CMV by the age of 40.
- CMV infection is usually mild, but it may be serious or fatal in those who are immunocompromised. Particularly at risk are low-birth weight infants and bone marrow and organ transplant patients.
- If a patient is at high risk of getting CMV diseases, blood that tests negative for CMV can be transfused.
- Alternatively, blood that has been filtered to decrease the number of white blood cells — the cells that carry CMV — will protect patients from getting a CMV infection from transfusion.
Transfusion-associated CMV (TA-CMV)

- TA-CMV infections have been recognized as a significant cause of morbidity and mortality in blood product recipients at risk

- These include
  - CMV-seronegative pregnant women
  - Premature infants born to CMV-seronegative mothers
  - CMV-seronegative allogeneic BMT recipients
  - CMV-seronegative patients with AIDS
Clinical spectrum

<table>
<thead>
<tr>
<th>Primary infection</th>
<th>Seronegative immunocompromised patient</th>
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<tbody>
<tr>
<td>Secondary infection</td>
<td>Seropositive patient infected with strain of virus</td>
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<tr>
<td>Reactivation</td>
<td>Latent seropositive patient reactivated</td>
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What We Can Do?

- Whether all seropositive blood donors can transmit CMV is unknown
- The use of CMV-seronegative blood products has been the ‘gold standard’ method of preventing TA-CMV infection
- It might be possible to reduce the risk of TA-CMV infection from asymptomatic seropositive donors by limiting the number of blood units transfused to subgroups of patients at high risk
- Improving the ability to detect IgM anti-CMV to identify acutely infected blood donors who may be more infectious than chronic carriers
- Perform selective or universal Leucocyte Depletion of Blood products
Leukocyte Depletion of Blood

Leukocyte depletion (LD) or Leukocyte reduction is a process applied to cellular blood components which removes a significant part of white blood cells from the product before it is transfused.
## Standards for LD Blood Components

<table>
<thead>
<tr>
<th></th>
<th>Blood component (WB, PRBCs)</th>
<th>RDP for pooling</th>
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</thead>
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<tr>
<td>American Association of Blood Banks (USA)</td>
<td>WB, PRBCs and Apheresis platelet</td>
<td>≤8.3 × 10⁵ WBC/Unit &lt;5 × 10⁶ WBC/Unit (red cell loss not more than 15%)</td>
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<tr>
<td>European Council criteria</td>
<td>&lt;1 × 10⁶ WBC/Unit (Hb &gt; 40/unit)</td>
<td>≤2.0 × 10⁵ WBC/Unit</td>
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<tr>
<td>Director General of Health Services (India) criteria</td>
<td>&lt;5 × 10⁶ WBC/unit (red cell loss not more than 10%)</td>
<td>&lt;8.3 × 10⁵ WBC/Unit</td>
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*RDP - Random donor platelets*
Other Strategies for Prevention of TA-CMV

• Use of frozen-deglycerolized RBCs prevents the transmission of CMV
• Transfusion of washed RBC (87% leukocyte removal) from CMV seropositive donors to neonates is associated with a lower frequency of anti-CMV seroconversion (1.3%) than that seen in recipients of unwashed RBC (13% to 35%)
Prevention of CMV through Filters

- Several studies – on use of leukocyte filters in preventing TA-CMV infection

- In a multicenter controlled trial, 21% of newborn infants transfused with unfiltered blood products developed CMV infection whereas no TA-CMV was observed in the group of infants transfused with LD blood products ($P = .005$)

- In one retrospective study, none of 59 CMV-seronegative patients with acute leukemia or non-Hodgkin’s lymphoma had evidence of seroconversion 2 months after transfusion with LD blood products
Prevention of CMV ..contd

- Retrospective study
  Only 2/13 CMV-seronegative patients who were transfused with lymphocyte depleted allogeneic bone marrow from CMV-positive donors, and who were transfused with LD CMV-unscreened blood products, developed clinical manifestations of CMV infection

- There are reports that leukocyte filters are capable of removing CMV-DNA from CMV-infected donor blood

- In a prospective randomized study in 487 patients undergoing BMT indicated that the use of LD blood products is equivalent to the use of CMV-seronegative blood products in preventing TA-CMV infection
Prevention of CMV...contd

- In the heart transplant setting, LD blood transfusion resulted in none of 17 (0%) patients receiving seropositive transfusions developing CMV infection, whereas 14 of 36 (39%) patients transfused with non LD seropositive blood became acutely infected
## CMV Infection – Seronegative Blood vs LD

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient Group</th>
<th>Transfusion Protocol</th>
<th>CMV Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bowden et al. (1995)</strong></td>
<td>Bone Marrow Transplant</td>
<td>Seronegative Blood</td>
<td>0.8%</td>
</tr>
<tr>
<td>Blood, 86, 3598-606</td>
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<tr>
<td><strong>Miller, 1991</strong></td>
<td>Bone Marrow Transplant</td>
<td>Seronegative Blood</td>
<td>4.4%</td>
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<tr>
<td>Bone Marrow Transplant, 7, 227-34</td>
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<tr>
<td><strong>Kumar et al. (1980)</strong></td>
<td>Neonates</td>
<td>Seronegative Blood</td>
<td>14.3%</td>
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<tr>
<td>Transfusion, 20, 327-31</td>
<td></td>
<td></td>
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<tr>
<td><strong>Gilbert et al. (1989)</strong></td>
<td>Neonates</td>
<td>Filtered</td>
<td>0%</td>
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<tr>
<td>Lancet, 1, 1228-31</td>
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<tr>
<td><strong>De Graan Hentzen et al. (1989)</strong></td>
<td>Leukaemics</td>
<td>Filtered</td>
<td>0%</td>
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<tr>
<td>Transfusion, 29, 757-60</td>
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<tr>
<td><strong>Van Prooijen et al. (1994)</strong></td>
<td>Bone Marrow Transplant</td>
<td>Filtered</td>
<td>0%</td>
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<tr>
<td>Br J Haematol, 87, 144-7</td>
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<tr>
<td><strong>Verdonk et al. (1987)</strong></td>
<td>Bone Marrow Transplant</td>
<td>Filtered</td>
<td>0%</td>
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<tr>
<td>Bone Marrow Transplant, 2, 73-8</td>
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What is Leukodepletion for?

- Reducing CMV infection by Leukodepletion

<table>
<thead>
<tr>
<th>Study</th>
<th>Without Filters</th>
<th>With Filters</th>
</tr>
</thead>
<tbody>
<tr>
<td>J. Haematol 70: 253-255, 1988</td>
<td>2/9</td>
<td>0/11</td>
</tr>
</tbody>
</table>

CMV Infection (%)
Who needs to receive CMV negative blood components?

- Intra-uterine transfusions
- Neonates up to 28 days post expected date of delivery
- Pregnancy:
  - Elective transfusions during pregnancy
    (not during labour or delivery)
- Adults and children post haemopoietic stem cell transplantation for all patient groups, including negative donors and recipients
- Solid-organ transplant recipients
- Severely immunosuppressed patients
- Congenital immunodeficiency patients
- HIV-infected patients
Preparation of LD Components

- During blood component preparation, the majority of leukocytes (90%) remain with the red blood cells (RBCs)
- Platelet concentrates retain ~8% of the initial leukocytes
- 2% are present in the plasma before freezing
Mechanisms of Filtration

- High-performance filters designed to remove leukocytes
- The plastic housing that contains the filtration medium is designed so that blood encounters a large surface area of medium
- The volume of blood retained by the filter (hold-up volume) is minimal
- Depletion of leukocytes is done depending on pore size
Timing of LR is Important

Filter Inline Bag

Lab Side Filter

TSCD
LD Filtration can be done:

**BEDSIDE - During transfusion**

- Does not prevent storage changes related effects, cannot assess product quality
+ Reduces cost as used only for selected patients

**LABORATORY – Before issue from Blood Bank**

- Does not prevent storage related changes, delay before issue
+ Better standardization/quality, reduced cost as only for selected patients

**PRESTORAGE – Inline, before component separation**

- Cost escalation unless ULR
+ Better standardization/quality, reduces NHFTR, alloimmunization & Plt. refractoriness
Pre-storage Leucoreduction is Recommended

- ↓ risk of leucotropic virus transmission
  leucocytes disintegrate and release the intracellular organisms after 72 hours of storage

- ↓ risk of HLA-alloimmunization. Removes intact leucocytes.
  leucocyte fragments after storage can pass through filters and alloimmunize the recipient

- Prevention of NHFTR
Significance of LD for CMV Transmission

- Up to 60% to 95% of donor population is CMV-seropositive, and it may be difficult to maintain sufficient inventory of CMV negative red blood cells and platelets.

- In such situations, LD is at least equivalent to the provision of CMV-negative units in preventing CMV disease transmission.

- May be less expensive than maintaining a CMV-negative inventory.
Possible Strategies in Indian Scenario

- Population – 1.29 billion
- ~10 million units of Blood is collected per annum
- Need for Blood and its components is increasing
- Large population of patients needs quality Blood components
- Universal Screening of CMV antibodies for Blood donors doesn’t seem to be realistic in our country
- Use of universal LD of Blood products to counter notorious creatures through pre-storage filters
 References

- Darrell J. Triulzi.et al., Chapter 16:“Leukocyte-Reduced Blood Components : Laboratory and Clinical Aspects” : Rossi’s Principles of Transfusion Medicine,2009,Fourth Edition,Wiley-Blackwell,Chichester , West Sussex,PO19 8SQ, UK
- Paglino JC .et al., ‘Reduction of febrile but not allergic reactions to red cells and platelets following conversion to universal Prestorage leukoreduction’, Transfusion. 2004;44:16–24