Prevention of transfusion-transmitted cytomegalovirus (CMV) infection: Standards of care


Providing high-quality, safe products is an essential mandate of blood operators. The use of cytomegalovirus (CMV)-safe products is one of the many decisions that must be made when clinicians order transfusions. The issue of CMV transmission by blood products was first addressed in a Vox Sanguinis International Forum in 1984 [1], well before the introduction of leucofiltration. In 2001, experts from the CMV Consensus Conference reviewed the literature and developed recommendations for the use of CMV-negative blood products for high-risk populations [2]. More than ten years later, significant variability in interpretation and application of the consensus statements has led to disparate local policies at both the hospital level and the blood operator level, nationally and internationally. Given the apparent discrepancies in risk mitigation for CMV transmission, it was of interest to assess the current practice for the prevention of transfusion-transmitted CMV (TT-CMV) internationally (Table 1). Further interest in CMV risk management strategies has been sparked by the implementation of pathogen reduction schemes and (universal) leucoreduction of cellular products in various countries. Thus, a repetition of an International Forum on this topic was warranted. Herein, we attempt to provide a snapshot of the wide range of practices related to donor testing of CMV, the use of CMV-negative products in specialized populations and the impact of this product line on inventory management.

The following questions were sent to experts in the field.

Question 1 – Established policy in the country

- Which practice is currently used in your country/centre when prevention of post-transfusion CMV is indicated?
- Are published national guidelines available or is the policy determined locally?
- Are treating physicians following this policy?
- Does the policy differ between types of facility (academic centre and community centre) or between different states/provinces/territories?
- Whose responsibility is it to order CMV-negative product – transfusion medicine service or the clinicians?
- Have you considered or implemented other methods to prevent post-transfusion CMV such as pathogen reduction technologies?

Question 2 – Specialized populations requiring CMV-negative products

- For which patient groups is prevention of post-transfusion CMV essential? Are these criteria strictly followed?
- Do you think that your policy related to use of CMV-safe products should be changed for certain populations? If so, which?
- What is the duration that CMV-safe products are supplied in these special populations?
  - Stem cell transplant
  - Neonates (please define age of neonate at your centre)
  - Solid organ transplants
  - Other specialized populations

Question 3 – Donor testing for CMV

- How are blood donors tested?
- Is your centre contemplating the implementation of nucleic acid testing for CMV?
- What is the frequency of transfusion-transmitted CMV at your institution?
- If you are producing blood products, what percentage of your donor base is CMV negative?
If your institution uses CMV-negative products, do you have challenges with maintaining an adequate inventory of CMV-negative products?

**Question 4 – Leucoreduction strategies**

- When leucoreduction is used to mitigate the risk of CMV transmission, is it done at bedside or at the production stage (prestorage)?
- What is the acceptable level, in terms of white blood cells per unit, which renders components 'CMV safe'?

**Question 5 – Policy modification**

- Do you think that serological screening for CMV can be abandoned when (universal) leucoreduction or pathogen reduction in blood products is applied?
- If you are in a jurisdiction that has options for both CMV-negative products and leucoreduced products, do you feel that clinicians working with your institution would oppose a policy of universal leucoreduction or pathogen reduction alone to prevent CMV?

**Question 6 – Future research**

- Do you think additional studies are needed to improve strategies for preventing post-transfusion CMV infection? If yes, please indicate your suggestions (systematic review, consensus conference).

### Summary of responses

We received responses from 21 organizations representing 18 countries. The respondents represent a variety of different types of institutions, from large centralized single-provider national systems to smaller regional hospital-based blood services.

There are some common themes related to the use of CMV-negative and leucoreduced products in all countries. All respondents commented on the primary goal of patient safety while attempting to balance issues such as cost and product scarcity. Many reported challenges related to the limited research available to aid in decision-making.
In the majority of the centres, leucodepleted products are available; however, universal leucodepletion is not performed at every facility. Most centres continue to have a dual inventory and provide both leucoreduced and CMV-sero-negative products to selected high-risk populations. Interestingly, the few centres that do not have dual inventories have a relatively high prevalence of CMV-sero-positive blood donors within their regional population. Most respondents have considered the implementation of pathogen reduction technologies to prevent transfusion-transmitted CMV (TT-CMV), but only a few organizations have implemented such strategies to further reduce the risk. Current limitations of these technologies include lack of an available strategy for PRBCs as well as cost restrictions.

Although most participants identified high-risk groups requiring specialized blood products, and policies related to the optimal choice for these groups varied worldwide. Practice included the use of leucoreduced products alone or the use of both leucoreduced and CMV-sero-negative products, the so-called belt and suspenders approach. There was a lack of consensus regarding who should receive specialized products. Some countries provide products that are both CMV negative and leucoreduced for neonatal, intrauterine transfusions and pregnant mothers only; other sites provide CMV-negative and leucoreduced products for all risk groups, while other sites provide leucoreduced products alone as they do not assess donor CMV status due to the high prevalence of CMV-sero-positive blood donors locally. Given the limited number of high-quality studies in these specialized populations, the variability in practice is not surprising.

The duration of use of specialized products for high-risk populations also varied among respondents. For neonates, some centres used specialized products for 1 month, while others continued for a year. For stem cell transplant recipients, some centres used specialized products for 100 days post-transplant, while other centres continued them lifelong or until the patient seroconverted. Such policies appear to be established locally based on clinician preferences.

The majority of the centres use enzyme immunoassay tests (CMV IgG and IgM) to assess their donor’s CMV status. The remaining respondents do not test donor CMV status routinely. Sites with higher prevalence of CMV in their population chose not to test their donors’ CMV status. Interestingly, there was substantial variation in the donor rates of CMV positivity ranging from 20% to 95%.

Few countries reported cases of TT-CMV, but all commented on the limitations of their voluntary haemovigilance systems. Challenges in meeting inventory demands were reported in a number of institutions, particularly for provision of compatible, CMV-negative, leucoreduced platelet support for HLA-alloimmunized patients.

When leucoreduction is used to mitigate the risk of CMV transmission, the majority of the centres perform this at the production stage. The acceptable leucocyte level, which renders a component as ‘CMV safe’, is \( <1 \times 10^6 \) residual leucocytes per unit.

Respondents did not reach consensus about whether serologic screening for CMV could be abandoned when leucoreduction or pathogen reduction in blood products is applied. Although some felt that there was sufficient evidence that universal leucodepletion rendered serologic screening for CMV unnecessary in many circumstances, numerous respondents still felt that there was insufficient data to abandon serologic screening altogether. A minority of responding centres use CMV-safe products alone for high-risk patients, as they have abandoned serologic testing due to high rates of CMV sero-positivity within their population. Many centres anticipate that pathogen reduction technology will become widespread as data accumulate regarding its efficacy and safety.

The majority of participants emphasized the importance of future research to guide practice. Although most experts would like to establish the residual risk of TT-CMV infection from either CMV-screened or leucoreduced blood products, most felt that this type of study would require large numbers of patients to show convincing results making the study impractical. Some suggested studies to assess the incidence of window-period donations as well as continued close monitoring of haemovigilance data following use of CMV-safe (leucoreduced) products. Others did believe that improved filters and the current literature provide adequate evidence regarding the equivalence of using leucoreduced products alone.

There are limitations to this survey. Respondents varied widely with respect to their position in the transfusion chain and included blood operators and transfusion medicine directors, who may or may not also be treating clinicians. In some cases, only one centre without a national operation was surveyed regarding the practice in the entire country; thus, the response may not actually reflect practice countrywide.
Respondents continue to struggle with the balance between safety, cost and scarcity of blood products. The combination of recent literature supporting the equivalence of CMV-safe and CMV-negative products as well as the implementation of universal leucoreduction has led to changes in policy at some centres. The literature suggests that both leucoreduced and CMV-sero-negative units have a very low residual risk of TT-CMV. CMV-sero-negative products are able to transmit CMV because the window period after infection until the antibody screening test becomes positive is 6–8 weeks. Leucoreduced units can transmit CMV because of the incomplete removal of white blood cells in a very small proportion of units (failure rate estimated at 0.2%). These two strategies are not additive, as window-phase seroconversions are associated with cell-free CMV in the plasma, which is not removed by leucoreduction [3, 4]. Less than one percentage (0.13%) of CMV-sero-negative units have detectable CMV DNA due to primary seroconversion, with some CMV experts recommending that the safest CMV product would be from selection of CMV-sero-positive donors at least 1 year after seroconversion [5]. One may argue that the blood system internationally is spending an excessive amount of funds on CMV testing with little or unquantifiable improvement in safety. Perhaps allocating these resources towards the management of other adverse transfusion reactions would provide a measurable improvement in safety.

The continued utilization of CMV-sero-negative blood products has both logistics and financial implications. Risk reduction measures are available, but are balanced in different ways by different blood systems. Limited availability of donors and inventory has led to some centres accepting products that are leucoreduced alone for high-risk immunocompromised patients; fortunately, reported cases of TT-CMV infection have not increased at those centres. Other centres report that when faced with decisions regarding age of blood product, ABO compatibility or CMV status, CMV status seems to be the attribute that many physicians feel can be most easily relinquished. Although this does not provide evidence-based research regarding the optimal decisions for high-risk patients, it may provide some reassurance to centres that are utilizing such protocols. Currently, international guidelines related to TT-CMV in high-risk patients do not exist. Overall, this survey highlights that while many centres are becoming more comfortable using CMV-safe products for high-risk adult transplant patients, many continue to order CMV-sero-negative leucoreduced products for high-risk neonates, intrauterine transfusions and pregnant patients. Future international collaborative studies that compare rates of TT-CMV infection following use of CMV-safe and/or CMV-negative products may aid in providing additional evidence in this field. There is a clear need to collect the data necessary to develop international guidelines for CMV risk management.

References

Question 1

• Within Australia, both CMV-negative and CMV-safe blood components are available.

All red cell and platelet components supplied by the Australian Red Cross Blood Service are leucodepleted at the production stage (i.e. prestorage). The Blood Service also performs CMV serology testing on selected blood donors to identify CMV-sero-negative blood donations.

• The Australian and New Zealand Society of Blood Transfusion (ANZSBT) Guidelines for Pretransfusion Laboratory Practice [1] provide guidance on the use of CMV-safe blood components in the following clinical settings:
  ○ For transfusion in pregnancy, the guidelines state that the use of ‘CMV-antibody-negative or CMV-safe (i.e. leucocyte-depleted)’ blood components ‘should be dictated by local or national policies’.
  ○ For transfusion of the fetus and neonate, the guidelines require that cellular components should be ‘CMV antibody negative and/or leucodepleted’ and that the use of these components ‘should be dictated by local or national policies’.
  ○ For recipients of allogeneic haemopoietic stem cell grafts, the guidelines require that all cellular components ‘should be CMV negative where indicated’.

The Australian Red Cross Blood Service currently recommends the use of CMV-negative cellular blood components for the following patient groups:

• CMV-sero-negative recipients of allogeneic or autologous stem cell, bone marrow or solid organ transplants;
• CMV-sero-negative recipients of highly immunosuppressive chemotherapy, for example, leukaemia and lymphoma;
• Recipients of intrauterine red cell transfusions;
• Premature (<1500 g) or immunocompromised neonates; and
• CMV-sero-negative pregnant women who require transfusion.

Further to this, the Blood Service also recommends the following for indications where CMV-negative blood components are required:

1. Select CMV-sero-negative components whenever possible;
2. If not available, leucodepleted components are considered to offer a high level of safety in preventing CMV transmission, but are not universally believed to be equivalent to CMV-sero-negative components; and
3. Careful monitoring for CMV infection and disease in high-risk patients.
4. Clinical practice with respect to the use of CMV-negative and CMV-safe blood components is variable as it is largely dictated by local policies.

In a recent survey of health professionals undertaken by the Blood Service, 86-85% of respondents (32 out of 37) indicated that their facility had a policy or guidelines for the use of CMV-negative blood components. The great majority (94-6%) believed that treating physicians did follow the policy/guidelines.

• Yes, the use of CMV-negative and CMV-safe blood components is largely dictated by local policies, which, in turn, are influenced by factors such as the range of services provided and patient case mix, as well as the experiences, preferences and opinions of the local clinicians.
• The responsibility for ordering CMV-negative components differs between facilities. Some transfusion medicine services routinely order CMV-negative components as part of their general stock orders; however, the majority only order CMV-negative blood components in response to specific patient requirements.
• The Blood Service is currently evaluating a number of pathogen reduction technologies with a view to possible future implementation; however, none have been implemented as yet.

Question 2

• The prevention of post-transfusion CMV is essential in the following patient groups:
  ○ CMV-sero-negative recipients of allogeneic or autologous stem cell, bone marrow or solid organ transplants;
  ○ CMV-sero-negative recipients of highly immunosuppressive chemotherapy, for example, leukaemia and lymphoma;
  ○ Recipients of intrauterine red cell transfusions;
  ○ Premature (<1500 g) or immunocompromised neonates; and
  ○ CMV-sero-negative pregnant women who require transfusion.

All cellular blood components supplied by the Blood Service are prestorage leucodepleted, and thus, all the above patient groups receive CMV-safe blood components as a minimum; however, most facilities also provide CMV-sero-negative components for these patients.
All cellular blood components supplied by the Blood Service are prestorage leucodepleted, and thus, all patients currently receive CMV-safe blood components.

All cellular blood components supplied by the Blood Service are prestorage leucodepleted, and thus, all patients currently receive CMV-safe blood components.

**Question 3**

- The Blood Service tests selected blood donors for CMV IgG antibodies on the Abbott Diagnostics Architect platform (CMIA).

CMV antibody testing is performed on donors who have previously tested CMV antibody negative or who have not previously been tested, only if their current donation is suitable for platelet production.

- No.

- The exact frequency of transfusion-transmitted CMV in Australia is unknown.

The Blood Service only very rarely receives reports of suspected cases of CMV transmission. While recipient-triggered lookback is undertaken in these cases, transfusion transmission is often difficult to prove conclusively. The Blood Service does not routinely undertake donor-triggered lookback for CMV.

- Approximately 72% of the Blood Service’s currently active donor base (i.e. the total number of donors who have donated in the last 12 months) has been tested for CMV antibody. Of the tested donors, 43% are CMV antibody negative.

Thus, approximately 31% of the currently active donor base is known to be CMV negative.

- The Blood Service does experience challenges from time to time with maintaining an adequate inventory of CMV-negative components, particularly of platelet and Rh (D)-negative components.

In the 12-month period from 1 October 2011 to 30 September 2012, the Blood Service received specific orders for 91,493 CMV-sero-negative red cell components and 32,734 CMV-sero-negative platelet components, representing 10.6% and 22.6% of our total orders for red cell and platelet components, respectively. In comparison, for the same period, the Blood Service issued 204,090 CMV-sero-negative red cell components and 40,238 CMV-sero-negative platelet components, representing 25.6% and 29.9% of the total red cell and platelet components issued, respectively, noting that CMV-sero-negative components are issued in lieu of ‘CMV-untested’ components to avoid unnecessary outdating. Tables 1 and 2 show the comparative order and issue data for red cell and platelet components, respectively, by ABO and Rh (D) group.

**Question 4**

- All red cell and platelet components supplied by the Blood Service are leucodepleted at the production stage (i.e. prestorage).

- The Blood Service component specification for residual WCC for leucodepleted red cells and leucodepleted apheresis platelets is \(<1 \times 10^6\) white blood cells per unit in 90% of units tested. The component specification for residual WCC for leucodepleted pooled red cells is \(<1 \times 10^6\) white blood cells per unit in 90% of units tested. The component specification for residual WCC for leucodepleted pooled platelets is \(<5 \times 10^5\) white blood cells per unit in 90% of units tested.

<table>
<thead>
<tr>
<th>ABO Rh (D) group</th>
<th>Ordered</th>
<th>% Of total red cells</th>
<th>Issued</th>
<th>% Of total red cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>O Rh (D) positive</td>
<td>32,513</td>
<td>10.2%</td>
<td>77,911</td>
<td>25.3%</td>
</tr>
<tr>
<td>O Rh (D) negative</td>
<td>21,926</td>
<td>16.7%</td>
<td>27,719</td>
<td>28.6%</td>
</tr>
<tr>
<td>A Rh (D) positive</td>
<td>22,312</td>
<td>9.0%</td>
<td>62,200</td>
<td>25.6%</td>
</tr>
<tr>
<td>A Rh (D) negative</td>
<td>6,132</td>
<td>10%</td>
<td>14,213</td>
<td>25.8%</td>
</tr>
<tr>
<td>B Rh (D) positive</td>
<td>6,029</td>
<td>9.3%</td>
<td>14,483</td>
<td>23.0%</td>
</tr>
<tr>
<td>B Rh (D) negative</td>
<td>1,497</td>
<td>10.1%</td>
<td>3,055</td>
<td>24.2%</td>
</tr>
<tr>
<td>AB Rh (D) positive</td>
<td>776</td>
<td>4.9%</td>
<td>3,511</td>
<td>22.7%</td>
</tr>
<tr>
<td>AB Rh (D) negative</td>
<td>308</td>
<td>4.3%</td>
<td>999</td>
<td>23.9%</td>
</tr>
<tr>
<td>All groups</td>
<td>91,493</td>
<td>10.6%</td>
<td>204,090</td>
<td>25.6%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ABO Rh (D) group</th>
<th>Ordered</th>
<th>% Of total platelets</th>
<th>Issued</th>
<th>% Of total platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>O Rh (D) positive</td>
<td>14,075</td>
<td>22.4%</td>
<td>17,394</td>
<td>30%</td>
</tr>
<tr>
<td>O Rh (D) negative</td>
<td>3,735</td>
<td>22.9%</td>
<td>4,825</td>
<td>27.8%</td>
</tr>
<tr>
<td>A Rh (D) positive</td>
<td>10,950</td>
<td>23%</td>
<td>13,773</td>
<td>30.8%</td>
</tr>
<tr>
<td>A Rh (D) negative</td>
<td>2,419</td>
<td>25.9%</td>
<td>2,750</td>
<td>32.2%</td>
</tr>
<tr>
<td>B Rh (D) positive</td>
<td>1,277</td>
<td>17.3%</td>
<td>1,669</td>
<td>25.5%</td>
</tr>
<tr>
<td>B Rh (D) negative</td>
<td>156</td>
<td>14.3%</td>
<td>218</td>
<td>21.3%</td>
</tr>
<tr>
<td>AB Rh (D) positive</td>
<td>109</td>
<td>18.6%</td>
<td>137</td>
<td>51.9%</td>
</tr>
<tr>
<td>AB Rh (D) negative</td>
<td>13</td>
<td>19.1%</td>
<td>13</td>
<td>44.8%</td>
</tr>
<tr>
<td>All groups</td>
<td>32,734</td>
<td>22.6%</td>
<td>40,238</td>
<td>29.9%</td>
</tr>
</tbody>
</table>
platelets is $< 0.8 \times 10^6$ white blood cells per unit in 90% of units.

Blood Service process control data for residual WCC in red cell and platelet components tested during the 12-month period from 1 October 2011 to 30 September 2012 are presented in Table 3. During this period, 99.8% of all red cell components tested had a residual WCC $< 1 \times 10^6$ per unit. Of the 17 units that had a residual WCC $\geq 1 \times 10^6$, only one had a residual WCC $\geq 5 \times 10^6$, the threshold level most often quoted as being sufficient to render a blood component ‘CMV safe’ [2]. 99.2% of all apheresis platelet components tested had a residual WCC $< 1 \times 10^6$. None of the 40 units that had a residual WCC $\geq 1 \times 10^6$ had a residual WCC $\geq 5 \times 10^6$. 100% of pooled platelet components tested during the 12-month period had a residual WCC $< 1 \times 10^6$.

<table>
<thead>
<tr>
<th>Component</th>
<th>Number of units</th>
<th>Residual WCC ($\times 10^6$/unit)</th>
<th>Residual WCC ($\times 10^9$/unit)</th>
<th>Mean</th>
<th>1 SD</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red cells</td>
<td>795 365</td>
<td>9231</td>
<td>17</td>
<td>1</td>
<td>0.27</td>
<td>0.16</td>
</tr>
<tr>
<td>Apheresis platelets</td>
<td>53 572</td>
<td>5243</td>
<td>40</td>
<td>0</td>
<td>0.21</td>
<td>0.15</td>
</tr>
<tr>
<td>Pooled platelets</td>
<td>79 993</td>
<td>1613</td>
<td>0</td>
<td>0</td>
<td>0.31</td>
<td>0.01</td>
</tr>
</tbody>
</table>

WCC, white cell count; SD, standard deviation.

Some suggested studies include the following:
- Determination of the precise threshold level of residual white cell count that would render a blood component CMV safe;
- Assessment of the incidence of CMV seroconversion following transfusion of leucodepleted alone versus CMV-sero-negative alone versus CMV-sero-negative leucodepleted components versus established CMV sero-positive (i.e. CMV sero-positive for $>12$ months) leucodepleted components;
- Estimation of the residual risk of CMV transmission in leucodepleted alone versus CMV-sero-negative alone versus CMV-sero-negative leucodepleted versus established CMV-sero-positive (i.e. CMV-sero-positive for $>12$ months) leucodepleted components;
- Systematic review;
- Consensus conference.

References

1 Australian and New Zealand Society of Blood Transfusion: Guidelines for Pretransfusion Laboratory Practice, 5th edn. Sydney, NSW, ANZSBT Ltd, 2007

J. Wong & S. Benson
Australian Red Cross Blood Service
17 O’Riordan Street
Alexandria
NSW, 2015 Australia
Emails: jwong@redcrossblood.org.au; sbenson@redcrossblood.org.au

T. Raison
Australian Red Cross Blood Service
301 Pirie Street
Adelaide
SA, 5000 Australia
Email: traison@redcrossblood.org.au
J. Pink  
Chief Medical Officer  
Australian Red Cross Blood Service  
44 Musk Avenue  
Kelvin Grove  
Qld, 4059 Australia  
Email: jpink@redcrossblood.org.au

G. C. Leitner & M. Horvath

Our institute produces exclusively apheresis platelets donated from healthy volunteers. In our country, CMV testing is only prescribed for single-donor platelets. All other blood products are delivered as leucocyte-depleted blood components. Leucocyte-depleted and CMV-negative blood products are considered as equal [1]. Overall, prestorage leucocyte depletion of packed red blood cells (PRBCs) replaced bedside filtration or filtration on demand in 1999.

Question 1

- Currently all platelet products, produced at our institution, are leucocyte-depleted and pathogen-inactivated by the Intercept treatment. Before this pathogen reduction method was implemented, the CMV status of donors was tested serologically. If preventing post-transfusion CMV (TT-CMV) was strongly indicated, only platelets from serological CMV-negative donors were given. All other patients received leucocyte-depleted products form either CMV-positive or CMV-negative donors.
- The maximum admissible leucocyte content of single-donor apheresis platelets is $1 \times 10^6$ leucocytes per unit, which is published in national and international guidelines [2]. Additional measures for TT-CMV prevention are not specified.
- The clinically caring physicians follow this policy.
- This policy is generally accepted in the whole country.
- It is the responsibility of the clinicians to order CMV-negative products in consent with the transfusion medicine service.

Question 2

- Prevention of TT-CMV is essential for all patients after bone marrow transplantation (BMT), especially after allogeneic BMT, for immature and mature born children until 6 months [3, 4]. In special cases (i.e. children pre-BMT), the decision to give CMV-negative platelets is made by the clinician and the transfusion medicine service together.
- To my opinion, there is no need to change the policy for the use of CMV-safe products, especially as the pathogen reduction systems applicable on all blood components are ‘ante portas’.
- Patients with solid organ transplantations are not routinely supplied with CMV-negative, but with ‘CMV-safe’ products.
- Patients undergoing BMT receive CMV-negative platelets until complete haematological reconstitution and discontinuation of immunosuppression, at least for 2 years. Newborns, as mentioned above, are supplied with platelets from CMV-sero-negative donors until their 6th month. In all other cases, the decision to give CMV-negative platelets depends on the clinical situation.

Question 3

- We only perform serological donor testing, which is sensitive for IgM and IgG antibodies.
- We are not planning to implement a nucleic acid testing for CMV.
- We are not able to survey TT-CMV. Red cells are leucocyte-depleted, but not CMV-tested. In our hospital, red cell demand is about 10 times higher than that of platelet concentrates.
- We have about 50% of CMV-sero-negative healthy volunteers in our routine multicomponent donor pool.
- Before a pathogen reduction system was introduced, the stockpiling of enough CMV-negative platelets was sometimes a challenge, depending on the activities of our BMT units (adults, children)

Question 4

- In Austria, prestorage leucocyte depletion as part of the production is regulated by law.
- The accepted level of white blood cell contamination is $1 \times 10^6$ leucocytes/unit [2].

Question 5

- Yes, we think that the overall CMV screening of donors can be abandoned when pathogen reduction methods are routinely applied [5]. Whether or not leucocyte reduction suffice is not clear yet [3–5].
- At our institution, universal CMV testing is abandoned since an overall pathogen reduction method (PI) is introduced. We still perform CMV testing of new donors and respect the donors’ CMV immune status if CMV-negative products are required and PI cannot be applied. The clinicians are interested in the prevention of TT-CMV. The clinically caring physicians rely on our recommendations.
Question 6

• Double-blind randomized controlled studies to evaluate the effectiveness of leucocyte depletion and CMV negativity versus leucocyte depletion alone versus leucocyte depletion and PI are necessary to answer this question.
• A systematic review of the literature could also be useful, but most likely not sufficient for a final consensus. Therefore, I would recommend a central registry, which processes all CMV infections, which are reported in connection with blood transfusions.

References

2 European Directorate for the Quality of Medicines & Health-Care: Guide to the Preparation, Use and Quality Assurance of Blood Components, 16th edn. European Committee on Blood Transfusion, 2010:280

G. C. Leitner & M. Horvath
Department of Blood Group Serology and Transfusion Medicine
University of Vienna
AKH Ebene 4i, Waehringerguertel 18-20
A – 1090 Vienna
Austria
Emails: gerda.leitner@meduniwien.ac.at;
michaela.horvath@meduniwien.ac.at

V. Compernolle

Question 2

All red blood cell concentrates and platelet concentrates distributed by the blood services are leukoreduced. Consequently, all patients benefit from lifelong CMV-safe blood products. The use of blood products that are both leukoreduced and CMV negative is limited to two indications, namely intrauterine transfusion and allogenic haemopoietic stem cell transplantation (given that both recipient and donor are CMV sero-negative). For the latter indication, lifelong CMV-negative plus leukoreduced products are used.

Question 3

In our blood service, a software-driven algorithm is used to select donors for further CMV testing. Serological screening for CMV includes IgM and IgG. Within our donor population, 136 516 donors are tested CMV positive, 261 518 donors are tested CMV negative, and 474 639 donors have never been tested for CMV. No major issues have been reported in maintaining an adequate inventory of CMV-negative products.

Given the generalized leukoreduction and the planned introduction of pathogen reduction technology, nucleic acid testing for CMV is not considered.

Question 4

Leukoreduction is systematically done during production (prestorage stage). Although 5 million white blood cells per unit is considered as CMV safe, acceptance limits during production are set at 1 million white blood cells per unit.

Question 5

We believe that serological screening for CMV can be abandoned when leukoreduction is combined with a pathogen reduction technology under the condition that the latter has a documented effectiveness against CMV.

Question 6

A systematic review comparing the effectiveness of CMV-negative versus CMV-safe blood products for patients are well accepted by the treating physicians who are responsible for ordering CMV-negative blood products. Both the blood services and the transfusion laboratories monitor an adequate use of these leukoreduced and CMV-negative blood products. The introduction of pathogen reduction technology for platelet concentrates will be obligatory from July 2013. After implementation of pathogen reduction technology, CMV testing for platelet concentrates is likely to be omitted.
undergoing allogeneic haemopoietic stem cell transplantation would be valuable.

V. Compernolle
Belgian Red Cross-Flanders
Blood Services
Ottergemsesteenweg 413
B-9000 Gent
Belgium
Email: veerle.compernolle@rodekruis.be

P. S. Prado Scuracchio & S. Wendel

**Question 1**
In February 2010, our centre implemented universal leukoreduction, and since then, we have been using white blood cell reduction for red cells or platelets not only when prevention of post-transfusion CMV is indicated.

There are published national guidelines available according to the Brazilian Ministry of Health, which state that CMV-sero-negative or leukoreduced components should be transfused in specific groups of patients at risk of developing life-threatening CMV disease [1].

Most services in Brazil follow this policy, but the real dimension of this practice is unknown, as well as the implementation of the universal leukoreduction.

The clinicians ultimately have the responsibility of ordering CMV-negative products; however, most centres that have implemented the universal leukoreduction components, audit all the transfusion requests in order to guide the best use of leukoreduced products.

We have not considered other methods to prevent post-transfusion CMV yet, such as pathogen reduction technologies, because although some methods (photo-chemical treatment with amotosalen and methylene blue) have already been licensed in Brazil, in practice, none has become available so far in this country.

**Question 2**
According to the Brazilian legislation, CMV-sero-negative or leukoreduced components with no distinction should be transfused in the following groups of patients:

- bone marrow transplantation (BMT), peripheral blood stem cells (PBSCs) or solid organ transplant recipients, which are CMV sero-negative.
- neonates with low birthweight <1200 g, whose mothers are CMV sero-negative or with unknown serological status.
- neonates requiring intrauterine transfusion.

We do not think we must change our policy related to the universal leukoreduction products, although some studies showed conflicting results for certain populations of recipients, for example, in neonates with low-birth-weight infants. In this group, the transfusion of units that are both sero-negative and leukoreduced would show a better efficacy in eliminating the transfusion-transmitted CMV, but cannot prevent the transmission of CMV in cases of blood donors in window phase and seroconverting who present high levels of free CMV virus in the plasma [2, 3].

**Question 3**
In our centre, blood donors are not tested for CMV since we implemented universal leukoreduced components in 2010; so no serological or nucleic acid testing for CMV is being done.

We do not have any case of transfusion-transmitted CMV in our institution before or after the implementation of the universal leukoreduction.

The percentage of CMV-sero-negative blood donors must be very low because in Brazil, studies of seroprevalence show very high percentages in the general population and blood donors, approximately 80–90%, depending on the region of our country, so it is very challenging to maintain an adequate inventory of CMV-negative products [4].

**Question 4**
Universal leukoreduction is done at the production stage, in the prestorage phase. We use red cell in-line filtration, so the products are filtered within 2 h after the collection.

The acceptable level of white blood cells per unit is <3–4 log of residual white blood cells, that is, 0.02 × 10⁶ white blood cells for platelets and 0.03 × 10⁶ white blood cells for red blood cells, with 99.99% removal of white blood cells.

**Question 5**
We think serological screening for CMV can be abandoned when leukoreduction or pathogen reduction in blood products is universally applied. A previous report from a single-centre prospective study in high-risk patients undergoing allogeneic haemopoietic stem cell transplantation using leukoreduced blood products not tested for CMV antibodies also demonstrated a low risk of transfusion-transmitted CMV [5].

In our institution, clinicians do not oppose a policy of universal leukoreduction since they recognize the benefits of this process and also because no cases of transfusion-
transmitted cytomegalovirus have been diagnosed until this moment.

**Question 6**

Strategies to improve the prevention post-transfusion CMV in our country include surveys of current practices and registered cases of transfusion-transmitted CMV infection in our country in order to know exactly the efficiency of universal leukoreduction or sero-negative CMV products especially in specific groups of risk and to verify whether there is the need to implement additional policies (e.g. improved leukoreduction quality control and/or CMV nucleic acid testing).

**References**


P. S. Prado Scuracchio
Attending Physician
Blood Bank of Hospital Sirio Libanes
Rua Adma Jafet, 91
São Paulo
Brasil 01308-050
Email: scuracchiop@ihsl.com.br

S. Wendel
Medical Director
Blood Bank of Hospital Sirio Libanes
Rua Adma Jafet, 91
São Paulo
Brasil 01308-050
Email: snwendel@terra.com.br

© 2013 International Society of Blood Transfusion
*Var Sanguinis* (2013)
since its inception in 2000. We reported to us or to the Quebec Hemovigilance System 0 cases of post-transfusion CMV infection have been reported to us or to the Quebec Hemovigilance System since its inception in 2000.

Question 2
All our cellular blood components are CMV safe. As stated above in section 1, we also supply CMV-negative products on request from hospitals. Although we feel that this recommendation of the Consensus Panel is reasonable, we have not set any policy concerning provision of such products. This policy is set locally by each hospital.

Question 3
We test donors for CMV antibodies on the automated blood screening instrument PK-7300 (Beckman Coulter) using the Beckman Coulter PK CMV-PA system. We tested 210 193 donations for CMV antibody from April 2011 to March 2012; of these, 198 936 (94–64%) were sero-negative.

Most tested donations were from repeat donations that had previously been screened negative for CMV antibody (donors screened positive for CMV antibody are not re-screened at subsequent donations).

In first-time donors, approximately 75% are screened negative for CMV antibody. We have no challenges in maintaining an adequate supply of CMV-negative products. We are not contemplating implementation of nucleic acid testing.

No cases of post-transfusion CMV infection have been reported to us or to the Quebec Hemovigilance System since its inception in 2000.

Question 4
All our blood components are leukoreduced before storage in our production laboratory.

In our quality control programme, all products must have <5 × 10⁶ residual leucocytes in the final container.

We tested 2867 red blood cell concentrates, 122 buffy coat platelet pools and 428 apheresis platelets from April 2011 to March 2012, and we had 100% conformity with our QC requirement. In fact, the mean residual leucocyte count was below 0·25 × 10⁶ in red blood cell concentrates and platelet products.

Question 5
Since the publication of the Consensus Conference Statement, no new data have been published that conclusively show the absence of incremental benefit of selecting CMV-sero-negative components for transfusion when all products are leukoreduced. A meta-analysis of the literature published in 2005 arrived at the conclusion that it was still appropriate to supply CMV-sero-negative/leukoreduced products particularly in the setting of bone marrow transplantations [5].

We have raised this issue with the transfusion medicine specialists who work in the hospitals we serve, and they are of the opinion that CMV screening and provision of CMV-sero-negative/leukoreduced cellular blood components should continue.

Question 6
In an ideal world, a properly designed clinical trial comparing leukoreduced cellular blood components to CMV-sero-negative/leukoreduced cellular blood components should be carried out. However, since the incidence of post-transfusion CMV infection is greatly reduced by component leukoreduction [6], the numbers needed to carry out such a trial, with sufficient power to detect a significant difference, render such a trial unfeasible.

References

© 2013 International Society of Blood Transfusion
Vox Sanguinis (2013)
In 2009, a survey comparing policies for CMV-sero-negative product provision by three separate academic transfusion services (in different provinces) to the recommendations made by the Canadian consensus document [1] was performed by myself to help formulate stronger recommendations via the National Advisory Committee on Blood and Blood Products. The only consistent recommendation with no caveats in all four documents was the provision of CMV-sero-negative products for the purposes of intrauterine transfusion. The next most concordant indication was for ‘current’ allogeneic haemopoietic stem cell transplant patients with an identified CMV-sero-negative donor. The policies were variable when the following indications were examined: neonates (up to 4 months of age); sero-negative pregnant women*, CMV-sero-negative patients likely to require allogeneic haemopoietic stem cell transplant and patients with HIV infection who were CMV sero-negative*. Some of the sites that were not providing CMV-sero-negative products according to the consensus conference identified at-risk populations* indicated that they were not provided with either a clinical request or sufficient diagnostic information to allow for identification of risk and hence provision of sero-negative product. In the centres evaluated, CMV-sero-negative products were not provided to solid organ transplant populations, but there was discrepancy in the interpretation of haemopoietic stem cell transplant requirements when six of Canada’s bone marrow transplant programmes were further surveyed. One of the six programmes recommended CMV-sero-negative products.
if the recipient was sero-positive, but the donor was CMV sero-negative. Four of the six programmes specified that the timing of request for CMV-sero-negative products should be made at the time of the diagnosis of a potentially transplantable disorder, regardless of whether or not a donor was identified. When asked about autologous stem cell transplants, four programmes recommended screening for CMV status and the provision of CMV-sero-negative products at the time of transplant. For all of the indications listed for CMV-sero-negative products, the provision of CMV-sero-negative products was for life or until documentation of seroconversion was present. For all of the non-transplant indications, the sites that indicated they would preferentially provide CMV-sero-negative products over CMV safe, the duration was until the age of 4 months in the neonatal setting, but no other clear durations of therapy were stated for pregnancy or HIV status. The National Advisory Committee on Blood and Blood Products is waiting for more evidence from proposed Canadian studies in the solid organ transplant and haematopoietic stem cell populations before finalizing national recommendations that would support the use of CMV-safe products in many of the indications listed above.

**Question 3**
Canadian Blood Services tests donors for the presence of anti-CMV IgM and/or IgG antibodies using passive particle agglutination on the automated Olympus PK-7300 microplate system. The proportion of donors tested will be determined by the number of CMV-sero-negative product requests placed to each particular centre, but on average, 45% of donor samples are tested for CMV. Donor-transmissible disease testing, including the serologic testing for CMV, has been localized to two Canadian Blood Services facilities in the country – one in Calgary and the other in Toronto. At this time, Canadian Blood Services is not considering the implementation of nucleic acid testing for CMV.

The local donor seroprevalence of CMV is variable depending on the region of Canada evaluated, but the combined donor seroprevalence has been stated to be 53% (verbal communication from L. Lieberman). In my local jurisdiction, the incidence of transfusion-associated CMV infection in solid organ transplant recipients who were CMV-sero-negative pretransplant and received an organ from a donor who was also CMV sero-negative was found to be 2.4% [2]. This study was performed prior to the implementation of universal leukoreduction and is in the process of being repeated with the current collection and blood product processing techniques.

The largest challenge I face is in the provision of compatible platelet support in patients who are HLA-alloimmunized, but also have a requirement for CMV-negative products on file.

**Question 4**
Since 1999, all red cell and platelet (whole-blood-derived and apheresis) cellular components produced by Canadian Blood Services have undergone prestorage leukoreduction. In the spring of 2005, implementation of buffy coat production in combination with continued prestorage leukoreduction was rolled out across the provinces served by Canadian Blood Services. Canadian standards require that 'whole blood or red cells from allogeneic donors shall be prestorage leukoreduced by a method shown to reduce the residual leukocyte count to \( < 5 \times 10^6 \) per component'. The same requirements are stipulated for pooled and apheresis platelets [3]. Despite these requirements, quality control data demonstrate that the average residual white cell data are \( < 1 \times 10^5 \) per red cell unit and \( < 0.05 \times 10^6 \) for platelet products (data provided by D. Howe, Canadian Blood Services).

**Question 5**
I do believe that there is sufficient evidence to support the abandonment of serologic screening for CMV in the setting of either universal leukoreduction or pathogen reduction. The study by Ziemann et al. [4] highlights the false sense of security with sero-negative components by demonstrating that 3% of donors who later demonstrated seroconversion had detectable CMV DNA despite a concurrent sero-negative result (window period).

In the Canadian provinces served by Canadian Blood Services, there has been varying amounts of opposition by clinicians to the abolishment of a CMV-sero-negative option. However, when placed with competing interests of ABO specificity, HLA typing and age of unit requests, the requirement for CMV sero-negativity is often the first to be willingly abandoned. Presentation of data demonstrating the current degree of leukoreduction and the evidence for significant lack of transfusion transmission of CMV, in the setting of the overall cost to society, will make the decision much more palatable to clinicians.

**Question 6**
I believe that the largest area of ongoing controversy with respect to CMV transmission appears to be with respect to fetal and neonatal transmission. Prospective monitoring for transfusion-associated CMV transmission and accurate prenatal testing programmes may facilitate more comfort in substituting CMV-safe products for this vulnerable population.
References


3 Canadian Standards Association. CAN/CSA Z902-10 Blood and Blood Components. Published February 2010


S. Nahiriak
Alberta Health Services
4B4.27 Walter Mackenzie Health Sciences Centre
8440-112 Street
Edmonton
Alberta, Canada T6G 2B7
Email: susan.nahiriak@albertahealthservices.ca

X. Dongfu

**Question 1**

1.1 Which practice is currently used in your country/centre when prevention of post-transfusion CMV is indicated?

A The main strategies related to prevention of transfusion-transmitted CMV in our blood centre are leukoreduction and virus inactivation.

1.2 Are published national guidelines available or is the policy determined locally?

A No, there isn’t national guideline or the local policy related to CMV.

1.3 Are treating physicians following this policy?

A No, see the reply above.

1.4 Does the policy differ between types of facility (academy centre and community centre) or between different states/provinces/territories?

A No, see the reply above.

1.5 Whose responsibility to order CMV-negative products: the transfusion medicine service or the clinicians?

A Clinicians.

1.6 Have you considered or implemented other methods to prevent post-transfusion CMV such as pathogen reduction technologies?

A Yes, we have implemented virus-inactivated technology in plasma products.

**Question 2**

2.1 For which patient groups is prevention of post-transfusion CMV essential? Are the criteria for these groups strictly followed?

- Infants born to CMV-sero-negative mothers who have no protective antibodies.
- CMV-sero-negative children receiving bone marrow or solid organ transplants from CMV-positive donors.
- Children with congenital or acquired immunodeficiency.
- Fetuses receiving intrauterine transfusions

The criteria of CMV for those groups aren’t yet strictly followed.

2.2 Do you think your policy related to the use of CMV-safe products should be changed for certain populations? If so, which and why?

A We think that more rigorous criteria should be followed for children with congenital or acquired immunodeficiency.

2.3 What is the duration that CMV-safe products are supplied in these special populations?

- Stem cell transplant patients and solid organ transplant patients: between 2 to 4 weeks before transplant and 100 days after transplant.
- Infants: from birth to 1 year post-natal.

**Question 3**

3.1 How are blood donors tested?

A No regular CMV testing for blood donation.

3.2 Is your centre contemplating the implementation of nucleic acid testing for CMV?

A No, not yet.

3.3 What is the frequency of transfusion-transmitted CMV at your institution?

A There has been no relevant data available.

3.4 If you are producing blood products, how much percentage of your donor base is CMV negative?

A About 5%.

3.5 If your institution uses CMV-negative products, do you have challenges with maintaining an adequate inventory of CMV-negative products?

A Yes, because CMV-sero-negative donors may be inadequate to fill the needs for CMV-safe blood products.
**Question 4**

4.1 When leukoreduction is used to mitigate the risk of CMV transmission, is it done at the bedside or at the production stage (prestorage)?

A At the production stage.

4.2 What is the acceptable level, in terms of white blood cells per unit, which renders components 'CMV safe'?

A The acceptable level of white blood cells per unit is \( <1 \times 10^6 \).

**Question 5**

5.1 Do you think that serological screening for CMV can be abandoned when (universal) leukoreduction or pathogen reduction in blood products is applied?

A No, there are some studies suggesting that CMV-sero-negative components may be more efficacious than leucocyte-reduced components in preventing CMV infection.

5.2 If you are in a jurisdiction that has options for both CMV-negative products and leukoreduced products, do you feel that clinicians working with your institution would oppose a policy of universal leukoreduction or pathogen reduction along to prevent CMV?

A May be.

**Question 6**

6.1 Do you think additional studies are needed to improve strategies for preventing post-transfusion CMV? If yes, please indicate your suggestions.

A Yes, it is needed that the pathogen reduction technology be used for red cell products and platelets product.

---

**X. Dongfu**

Transfusion Service  
Shanghai Blood Center  
Hongqiao Road  
1191 Shanghai  
China  
Email: xiedongfu@sbc.org.cn

---

**T. Krusius, E. Juvonen & S. Sainio**

Finnish Red Cross Blood Service is responsible for the national blood programme in Finland. Finnish Red Cross Blood Service is the exclusive provider of blood products in Finland. Quality and safety of blood products comply with EU Directives and the standards and recommendations given by the Council of Europe in the Guide to the Preparation, Use and Quality Assurance of Blood components.

Anti-CMV screening of blood donors was introduced in 1984. Eighty per cent of donors were anti-CMV positive. Indications of transfusion of CMV-negative blood products were transfusions to preterm neonates and allogeneic, CMV-negative stem cell transplant recipients with a CMV-negative donor.

Production of red cells and platelet products by the buffy coat process after overnight hold was gradually introduced by the Finnish Red Cross Blood Service in the early 1990s. When good quality and consistently efficient leukodepletion filters both for red cells and platelets became available and scientific evidence from randomized clinical studies had been published, CMV-negative blood products were replaced by leukodepleted blood products. Since 1994, no CMV-negative blood products have been supplied by the Finnish Red Cross Blood Service. There have been no reports on suspected transmission of CMV by leukodepleted blood products.

Universal leukodepletion of platelet products was introduced in Finland in 2000 and universal leukodepletion of red cell products in 2003.

Similarly, based on a risk assessment that took into account the low prevalence and incidence of HTLV infections in Finland and efficient removal of leucocytes by filtration, Finnish Red Cross Blood Service terminated screening of blood donors for HTLV I and II antibodies in 2008.

**Question 1**

All blood products provided to hospitals in Finland are leukodepleted. Transmission of CMV is prevented by removal of leucocytes by filtration [1]. This is a national policy. CMV-negative blood products are not available. Pathogen inactivation of platelet products has been considered in general by the Finnish Red Cross Blood Service, but has not been implemented due to several reasons.

**Question 2**

All blood products are leukodepleted. There are no special patient populations who would additionally require CMV-negative blood products.

**Question 3**

Screening of blood donors for antibodies to CMV was introduced in 1984. Because the proportion of CMV-negative donors was low (20% in late 1980s) and because new infections occurred in the CMV-negative donor population, maintaining an adequate inventory of CMV-negative blood products was costly and laborious.

**Question 4**

Prestorage leukofiltration is performed. All blood products are leukodepleted. Number of residual leucocytes...
complies with EU Directive and the Council of Europe Guide to the Preparation, Use and Quality Assurance of Blood components.

The primary collection pack including the leukodepletion filter is rigorously validated before introduction to routine use. Furthermore, 1% of red cell and platelet products are analysed for residual leucocytes as quality control using a flow cytometry-based test. The average number of leucocytes \((\pm 2 \text{ SD})\) was \(0.03 \times 10^6 (0–0.13 \times 10^6)\) in red cell products and \(0.04 \times 10^6 (0–0.41 \times 10^6)\) in platelet products in 2012. In all analysed red cell or platelet products \((n = 2859\) and \(n = 555\), respectively), the number of residual leucocytes was \(<0.5 \times 10^6\) in 2012.

**Question 5**
Clinical studies and long experience from several countries, including Finland, indicate that CMV-negative red cell and platelet products can safely be replaced by leukodepleted products.

**Question 6**
The quality and efficacy of leukodepletion filters has improved and most likely will further improve in the future [2]. Therefore, the risk of transmission of CMV by leukodepleted blood products has further decreased since the time of the first clinical studies on transmission of CMV by leukodepleted blood products. Several recent studies confirm that leukodepleted blood products do not transmit CMV infections [3–6]. According to our opinion, there are enough data from clinical studies on the safety of leukodepleted blood products in the prevention of CMV transmission. No further studies are needed.

**References**


**J.-P. Cazenave, P. Guntz, D. Kientz, G. Andreu & P. Morel**

**Question 1**
Universal leucocyte reduction is currently used in France and has been implemented in 1998 for all red blood cell concentrates and all platelet concentrates transfused to patients and in 2001 for therapeutic plasma.

In addition to leukoreduced blood components, the use of cellular products from CMV-sero-negative donors is recommended in specific situations: allogeneic haemopoietic stem cell transplantation when donor and recipient are CMV negative, lung transplantation when donor and recipient are CMV negative and newborn with CMV-sero-negative mother.

National guidelines published by AFSSAPS/ANSM (Agence nationale de sécurité du médicament et des produits de santé) are available. Usually treating physicians follow strictly the recommendations. These guidelines are the same for the whole country.

Transfusion protocols are followed both by the transfusion medical service issuing blood components and the clinicians ordering ‘CMV-negative products’.

Pathogen inactivation of platelet concentrates (apheresis or pooled buffy coats) using amotosalen and UVA (Intercept Blood System™; Cerus, Amersfoort, the Netherlands) is already in place in four of the 17 regional transfusion centres, Alsace [1] and French overseas departments (Réunion [2], Martinique, Guadeloupe, Guyane).

**Question 2**
Prevention of post-transfusion CMV is considered essential in France for the following patient groups: (1) stem cell transplant patients (if donor and patient are CMV negative), (2) lung transplant patients (if donor and patient are CMV negative), (3) premature babies
(<32 weeks, if the mother is CMV negative) and all neonates, and (4) CMV-negative pregnant women.

The criteria for prevention of post-transfusion CMV are strictly followed in these special groups of patients. They all are transfused with leukoreduced cellular blood components either from CMV-sero-negative donors or treated for pathogen inactivation by amotosalen–UVA.

Seventeen post-transfusion CMV infections have been reported by the French Haemovigilance network between 2000 and 2011. As no full analysis of these cases has been released, this information is of no help to estimate the need to change the present national policy.

In these special populations, the duration that CMV-safe cellular blood components are transfused varies. The transfusion protocols with CMV-safe products are for lifetime to stem cell transplant patients and solid organ transplants patients, such as lung transplantations. The transfusion of CMV-safe products for neonates is during the first month of life and all along pregnancy for CMV-sero-negative women.

**Question 3**
Donors are tested for CMV using serological assays (total anti-CMV IgG and IgM antibodies). When a donor is tested positive, his status is definitively positive, even if, later, the result of a serology test is negative.

Implementation of nucleic acid testing for CMV is not contemplated in France at the moment.

In our institutions, we recorded no case of transfusion-transmitted CMV infection, at least in the past 5 years.

The frequency of the French CMV-negative donor base is around 67% for men and 60% for women.

In general, there is no challenge to maintain an adequate inventory of CMV-negative products. Four French regional transfusion centres are providing clinicians with pathogen-inactivated platelet concentrates instead of CMV-sero-negative platelet concentrates.

**Question 4**
Universal leucocyte reduction is only done by prestorage filtration. White blood cell content must be <10⁶/blood component. This level is mandatory and must be guaranteed for more than 97% of each blood processing laboratory in France.

**Question 5**
We consider that leukoreduction is efficient, but does not allow stopping the serological screening, that the pathogen inactivation technology we use (amotosalen–UVA) for platelet concentrates is efficient to prevent transfusion-transmitted CMV infection and that, if so, CMV serology can be abandoned for platelet concentrates [3]. We have already provided extensive information for the clinicians before implementation of pathogen inactivation in the regions where amotosalen–UVA-treated platelet concentrates are provided, and have received full approval for change.

**Question 6**
In the context of pathogen inactivation, there is no additional study/development needed to prevent transfusion-transmitted CMV with platelet concentrates.

Pathogen inactivation will probably not be available for the next 5–10 years for routine use of red blood cell concentrates. Failure of both leukoreduction and CMV-negative products, although rare, has been clearly identified. It seems mainly related to primo-infection in donors, where free virus can be observed in plasma (which can explain leukoreduction failure) during the serologic window period (which can explain CMV-negative failure). Therefore, as free CMV is almost never observed in stable CMV-positive IgG + IgM individuals, and considering the extremely low failure of present leukoreduction techniques, investigation of transfusion-transmitted CMV prevention, using CMV IgG + IgM-sero-positive donors known for more than a year may be interesting for the whole community, as it could be a serious option in places where CMV prevalence is high in the population.

**References**


J.-P. Cazenave, P. Gunzt, D. Kientz

Etablissement Français du Sang (EFS)-Alsace

10, rue Spielmann, BP36

67450 Cedex Strasbourg

France

Email: jean-pierre.cazenave@efs.sante.fr

G. Andreu

Institut National de la Transfusion Sanguine (INTS)

6, rue Alexandre Cabanel

75015 Paris

France

Email: gandreu@ints.fr

© 2013 International Society of Blood Transfusion

*Vox Sanguinis* (2013)
Question 1
In Germany, since the year 2001, leukoreduction of red cell concentrates and platelet concentrates is mandatory. Because the introduction of leukoreduction has been mandated by a federal authority (Paul Ehrlich Institute), it has to be performed nationwide by all blood donor services. Furthermore, until recently, only donations sero-negative for HCMV were used for at-risk patients. However, there has been a change in the strategy to reduce the risk of transfusion-transmitted HCMV. The updated guidelines now suggest not to actively select HCMV-sero-negative donations for the production of leukoreduced blood components.

However, because it is difficult to convince the clinicians to follow this new strategy, our blood donor service has not discontinued testing for anti-HCMV so far.

Some German blood donor services implemented a minipool nucleic acid testing for HCMV in order to identify infective donors during the preseroconversion window period. Another strategy that is discussed to improve safety for at-risk patients is to use blood components from donors, which are for at least one year HCV antibody reactive and HCMV nucleic acid testing negative.

Question 2
For patients with bone marrow or stem cell transplantation, the strategy is that HCMV-antibody-negative patients should be transfused with HCMV-negative blood components and HCVM-antibody-positive patients with HCVM-positive blood components, in order to prevent HCMV infections or HCMV reactivation. Other patients at risk are newborns, pregnant women and immunosuppressed patients.

Question 3
Currently, our blood donor service is testing all multiple-time donors with HCMV-antibody-negative results within the previous donations. Testing for HCMV antibodies is performed using a haemagglutination assay on the Beckman Coulter 7300 blood type analyser. Approximately 50% of our blood donors are CMV negative.

In case of a shortage in HCMV-negative products, we test multiple-time donors who have not been tested for anti-HCMV in the past in order to expand our pool of anti-HCMV-negative donors.

The frequency of HCMV transfusion-transmitted infections is currently not investigated at our blood donor service, because we do not initiate lookback investigations after donor seroconversion. Serious HCMV infections in patients are very rare events.

Testing of all donations for HCMV DNA is feasible, but currently not planned. However, blood components that cannot be leukoreduced, that is, granulocyte concentrates, are already tested for HCMV DNA.

Question 4
In Germany, leukoreduction of red cell concentrates and platelet concentrates is mandatory. The leucocyte count must be lower than \(1 \times 10^6\) per unit. Data from our production department demonstrate that the residual concentration of leucocytes is even \(<1 \times 10^5\) per unit. Leucocyte filtration has to be performed at the production stage.

Question 5
There is currently no evidence that serological screening is beneficial when leukoreduction or pathogen reduction is in place. Rather there might be a risk to choose HCMV-sero-negative donations, because these donations are at higher risk of being in the infectious antibody-negative window period. Although leucocyte reduction is established, clinicians are still asking for products that tested negative for HCMV.

Question 6
Based on our experience, comprehensive scientific study could be an important step to clarify the currently open questions about HCMV-safe blood products. The study should include donor-related as well as patient-related lookback investigations and examine the influence of leucocyte depletion, pathogen reduction methods as well as different screening methods (antibody testing, ID-nucleic acid testing as well as MP-nucleic acid testing) on blood safety.

E. Seifried
Medical Director
German Red Cross
Institute for Transfusion Medicine and Immunohematology
Sandhofstrasse 1
60528 Frankfurt
Germany
Email: e.seifried@blutspende.de
Question 1

- In Hong Kong, we routinely maintain an inventory of CMV-sero-negative red cells and platelet concentrates for patients with conditions necessitating treatment using the product. As a policy, if CMV-sero-negative blood products are not adequate to meet demands, which happened rarely, leucodepleted blood products are also considered as CMV safe for prevention of transfusion-transmitted CMV infection.

- The Hong Kong Hospital Authority (HA), which manages all the public hospitals in the territory, consumes about 90% of the blood components we supply. HA regularly reviews and updates its Transfusion Guidelines including the indications for CMV-sero-negative blood products. Hospitals in the private sector usually take reference to the HA’s Transfusion Guideline and set their guidelines individually.

- It is a standard procedure for hospital blood banks to check patients’ CMV status if CMV-sero-negative blood products are requested. Although there were no clinical audits undertaken to evaluate treating physicians’ compliance to the use of the products, as the products are routinely available, there is no question on the compliance.

- Generally, the policy of transfusing CMV-sero-negative or leucodepleted blood products for the prevention of post-transfusion CMV does not differ between types of facility.

- Orders for CMV-negative blood products are usually initiated by the patients’ attending doctors.

- Subsequent to a policy support in 2009, we have launched a project to move towards universal leucodepletion of blood products. In 2011, about 45% of the red cell concentrates we distributed to hospitals were leucodepleted. In 2012, we plan to gradually scale up the collection and supply of leucodepleted apheresis platelets. At the same time, we are exploring the application of pathogen reduction technology for buffy coat platelets.

Question 2

- According the latest edition of the HA’s Transfusion Guidelines, the following groups of patients are indicated for CMV-sero-negative blood components:
  1. CMV-antibody-negative pregnant women;
  2. CMV-antibody-negative recipients of allogeneic stem cell grafts;
  3. Intrauterine transfusions (IUTs);
  4. Patients with HIV infection.

  However, we also supply CMV-sero-negative blood components to indications according to international guidelines, such as infants weighing <1.5 kg, and there was an increasing trend of requesting for CMV-sero-negative or CMV-safe blood products for neonates and pregnant women irrespective of their serological CMV status. In collaboration with hospital blood banks, we prospectively evaluated the relevance of the indications for the products.

  - As mentioned above, infants weighing <1.5 kg, neonates and pregnant women should also be included in the HA’s Transfusion Guidelines. We monitor the latest international development on the prevention of transfusion-transmitted CMV infection in high-risk patients.

  - The duration of supply of CMV-sero-negative blood components is as follows:
    - Stem cell transplant recipients – as long as they are CMV sero-negative;
    - Neonate – first year of life
    - Solid organ transplant patients – this is not in the list of HA’s Transfusion Guidelines, but CMV-safe blood products are issued on special requests as long as the patients are CMV sero-negative.

Question 3

- Blood donation samples are tested for anti-CMV IgG by Microparticle Enzyme Immunoassay on Abbott AxSYM (Abbott Laboratories, Abbott Park, IL, USA) [1].

- We do not have a plan to implement nucleic acid testing for CMV at present.

- We do not have data on the frequency of transfusion-transmitted CMV.

- A local study showed that all adults (>21) in Hong Kong were CMV positive. It was estimated that the CMV sero-positivity rate among our donor population is approximately >90%. In the day-to-day selection of donor samples for anti-CMV assay after excluding those who have previously been tested...
positive, the frequency of CMV sero-negativity is approximately 65%.

- We generally do not have any problems in maintaining an adequate inventory of CMV-sero-negative red cells and platelets and can meet all demands for supply. In 2011, 9.6% and 6.6% of red cells and platelet concentrates supplied to hospitals were CMV sero-negative, and 100% and 98.8% of the demands for CMV-sero-negative red cells and platelet concentrates were met, respectively.

Question 4

- The great majority of leucofiltration activities take place at the production stage (prestorage) in the blood transfusion service.
- We adopt the Council of Europe Standard, which defines leucodepletion as residual leukocytes <1 × 10^6 per unit.

Question 5

- Although there was evidence in the literature that leucofiltration was an effective alternative for prevention of transfusion-transmitted CMV infection in bone marrow transplant patients [2], there were other views that considered the use of CMV-sero-negative blood components superior to leucodepleted CMV-non-tested products [3, 4]. We incline to maintain the CMV-sero-negative cellular blood component inventory for transfusion of indicated patients. Leucodepleted blood can supplement the supply when there is a shortage of CMV-sero-negative blood components. As for pathogen reduction technology, there were claims that treated platelet concentrates were equivalent to CMV-sero-negative products. Whether it can replace CMV serology test will depend on further high-confidence evidence and the comparison of the cost-effectiveness of both.
- In our view, it is inevitable that individual clinical users will hold different views regarding the safety of CMV-sero-negative, leucodepleted and pathogen-reduced blood products, especially during the early stage of policy change. Solid evidences from well-designed clinical studies will be useful in changing the mindset and practice of clinical users.

Question 6

- The peril of serological screening of blood donations for anti-CMV is primarily attributed to the rather long window period between CMV infection and seroconversion [1]. Ziemann and colleagues reported high prevalence of CMV DNA in newly sero-positive donors and surmised that transfusion of blood components from sero-negative donors could impose a higher risk of transfusion-transmitted CMV than leucodepleted products from donors who have been sero-positive for more than 1 year [5]. These data could potentially revolutionize the current strategy of using CMV-sero-negative blood components and the testing algorithm. We feel that further studies with higher confidence levels as well as controlled clinical trials are required to sustain the findings and the new paradigm of strategy for supply of CMV-safe blood products to high-risk patients.

References


C. K. Lin
15 King’s Park Rise
Yaumatei
Kowloon
Hong Kong
Email: cklin@ha.org.hk

J. O’Riordan

Question 1
Currently, both CMV-sero-negative and leucoreduced (LR) components are provided to prevent transfusion-
transmitted (TT) CMV in Ireland. There are no published national guidelines, so policy is determined locally. Clinicians decide which recipients require CMV-negative components. However, there is evidence from the recent Irish Blood Transfusion Service (IBTS) implementation of electronic ordering of components that some of the largest users of platelets, encompassing 37% of all platelet orders, order almost exclusively CMV-negative platelets (B Quirke, personal communication).

Pathogen reduction technologies were considered by the IBTS to reduce the risk of bacterial contamination of platelets, but not implemented because of cost considerations.

**Question 2**

Patients deemed at highest risk are as follows:

- CMV-sero-negative, allogeneic, haemopoietic stem cell transplant recipients.
- The fetus via intrauterine transfusion.
- Pregnant women, regardless of CMV serostatus.

Patient groups with moderate risk also included in TT-CMV risk reduction are as follows:

- CMV-sero-negative potential allogeneic stem cell transplant recipients.
- CMV-sero-negative autologous stem cell transplant recipients.
- Neonatal patients especially low-birthweight preterm infants who are the most transfused group of infants (Infants in their first month of life are typically defined as neonates).
- CMV-sero-negative recipients of solid organs (highest risk lung) from CMV-sero-negative donors.
- CMV-sero-negative HIV-infected individuals.

In practice, all of the above categories of patients receive CMV-negative and LR cellular components, and once assigned by clinicians, it would appear that policy does not change.

Granulocyte components that cannot be leucoreduced are sourced from CMV-sero-negative donors.

**Question 3**

Previously sero-negative and first-time donors are tested for CMV total antibody by enzyme immunoassay. There are no plans for the implementation of CMV nucleic acid testing.

Possible transfusion-transmitted diseases are reported and investigated through the National Haemovigilance Office, which was set up in 1999, and while acknowledging the limitations of a passive surveillance system, there have been no reported cases of CMV infection associated with transfusion.

A study of CMV seroprevalence and seroconversion in 2010 at the IBTS showed that overall, only 21.97% of a cohort of 95,642 blood donors were CMV-sero-positive, female gender correlated with sero-positivity \( P < 0.0001 \) and CMV prevalence rates rose from 12% in 18-20-year-old donors to 40% in 61-65-year-old women. CMV seroprevalence in first-time Irish donors was 16.38% in comparison with 56.73% for first-time donors born outside of Ireland (donors primarily originating from former Eastern European countries). The CMV seroconversion rate in 2010 was 0.61% (females 0.74% and males 0.52%).

The low CMV seroprevalence in donors is also seen in other Irish populations. A study of pregnant women \( n = 1047 \) attending a large Dublin maternity hospital showed that 30% of Irish women were CMV sero-positive in comparison with 56% of women from Western Europe and 97% from Africa [1]. Furthermore, only 21.3% of 296 Irish unrelated stem cell transplant recipients from 1993 through to 2012 were CMV-positive pretransplant in comparison with 81.8% of 33 recipients born outside Ireland (S Horgan, personal communication, Irish Unrelated Bone Marrow Registry).

There is usually a sufficient inventory of CMV-seronegative cellular components to supply the at-risk groups. However, even with a relatively bountiful supply of sero-negative donors, there can be challenges with supplying CMV-sero-negative apheresis platelets of the correct ABO D group, particularly in view of the already noted widespread overordering of CMV-negative platelets.

**Question 4**

Universal leucoreduction of IBTS blood components was implemented in 1999 primarily to reduce the risk of vCJD transmission.

Prestorage leucoreduction is performed; the quality standard for white blood cell (WBC) reduction is to achieve a WBC \(< 1 \times 10^6 \) cells per unit.

The residual leucocyte content for all apheresis platelets is counted.

In situations where the only available platelet component for human leucocyte antigen (HLA)- or human platelet antigen (HPA)-matched platelets is a CMV-sero-positive donation, a ‘CMV-safe’ component is issued provided that the residual WBC is within specification.

**Question 5**

There is usually a sufficient inventory of CMV-seronegative cellular components to supply the at-risk groups. However, even with a relatively bountiful supply of sero-negative donors, there can be challenges with supplying CMV-seronegative apheresis platelets of the correct ABO D group, particularly in view of the already noted widespread overordering of CMV-negative platelets.

Possible transfusion-transmitted diseases are reported and investigated through the National Haemovigilance Office, which was set up in 1999, and while acknowledging the limitations of a passive surveillance system, there have been no reported cases of CMV infection associated with transfusion.
the LR process using statistical process control is required. Two recent studies may shed some light on the reasons for breakthrough infections associated with either type of preventative strategy.

The residual risk of TT-CMV might arise from primary CMV infection in the donor as CMV DNA was reproducibly detected in plasma samples of some 44% of 82 newly sero-positive donors, with a range of 12–62% depending on the interval to the last sero-negative donation. Window-phase donations, that is, CMV DNA detection in the last sero-negative donation, were found in only 2 (2.9%) of 68 seroconversion cases. Latently infected donors (n = 598), who had been sero-positive for at least 1 year, tested negative for the presence of CMV DNA [3]. The authors suggest that donations from recently seroconverted donors should be excluded for immunocompromised patients and that the transfusion of WBC-reduced blood components from sero-negative donors could pose a greater risk of TT-CMV than transfusion of WBC-reduced blood from donors who have been sero-positive for at least 1 year. A follow-up study from the same group of investigators detected CMV DNA in a smaller proportion of donors (10%) who recently seroconverted, but the study describes a frequently prolonged course for primary CMV infection in 13 donors with CMV antigens and DNA detectable in peripheral blood for up to 54 and 269 days, respectively [4].

Currently, the IBTS’s ‘belt and braces’ approach excludes primary CMV infection in recently seroconverted donors, but not window-phase donations. If the findings of the above studies could be replicated by large-scale CMV DNA studies of blood donors, the IBTS would give consideration to recommending LR donations from CMV donors who have been sero-positive for more than 1 year as CMV safe. It is likely that clinicians would accept such a recommendation provided that the evidence base was endorsed by the recently constituted National Transfusion Committee, which is made up of the clinical users of blood.

Had pathogen inactivation of platelets been introduced, CMV serological screening for platelet components would have been abandoned.

**Question 6**
The efficacy and safety of combining serologically screened and LR components to prevent TT-CMV as compared to LR has not been studied in randomized controlled trials and is now being challenged as a less safe option than LR alone, as this practice may paradoxically increase the relative risk of transfusing cell-free viraemic units in window-phase CMV-negative donation as suggested in recent German Guidelines [5].

However, there is an ongoing large prospective birth cohort study in the USA examining the incidence of TT-CMV in low-birthweight infants who receive CMV-sero-negative plus LR blood components [6]; interim results presented by JD Roback at the American Association of Blood Banks Annual Meeting (Boston, MA, 6–9 October 2012) suggest that this is a highly effective strategy for this infant population.

The small residual risk linked with CMV serologically screened, LR or combined CMV-negative and LR components could be addressed by large-scale studies using sensitive CMV DNA nucleic acid testing of donors in conjunction with CMV serology to determine the following:

1. The incidence of window-period donations.
2. The duration of CMV DNAemia in the recently seroconverted.
3. Whether reactivation of CMV infection with viraemia occurs in latently infected asymptomatic donors, who have been CMV sero-positive for over 1 year.

**References**


J. O’Riordan
Irish Blood Transfusion Service
National Blood Centre
James’s Street
Dublin 8
Ireland
Email: joan.o.riordan@ibts.ie
Question 1
In our country, both leucocyte-reduced and CMV-sero-negative blood components are currently used for the prevention of transfusion-transmitted CMV (TT-CMV) infection. In our centre, taking into account the high prevalence of CMV sero-positivity in the Italian population (about 80%, www.epicentro.iss.it) and in agreement with international reports [1, 2], we decided to use filtration leukoreduction for red blood cells (RBCs) and platelets (PLTs). In particular cases where CMV transmission could cause significant clinical complications, mostly neonates and intrauterine transfusions, we utilize leukoreduced blood components from CMV-sero-negative donors.

Our national policy is described in guidelines published by Società Italiana di Medicina Trasfusionale ed Immunematologia (SIMTI Standard di Medicina Trasfusionale 1st Ed 2007; www.simti.it).

We are not aware of national studies carried out to determine physicians’ compliance with the national guideline. The Blood Transfusion Committee from our institution formally adopted the national guideline.

National guidelines apply to any facility.

In our setting, a written clinician’s order compliant to the guideline is required for CMV-safe products. Clinicians fill a form listing patient(s) with conditions requiring safe CMV treatment to the Blood Transfusion Service; an operator from the Blood Transfusion Service enters this information in the electronic data base.

So far, we have not routinely implemented pathogen reduction technologies or other methods to prevent TT-CMV.

Question 2
In agreement with international guidelines and based on our understanding of the scientific literature, prevention of TT-CMV infection is essential for patients severely immunodepressed such as CMV-negative patients receiving haemopoietic cell transplants or solid organ transplants from CMV-negative donors, newborns (<4 months), particularly in case of low-birthweight neonates and intrauterine transfusions, CMV-negative pregnant women and CMV-negative HIV patients.

We do not expect to change our policy in the near future.

For haemopoietic or solid organ transplant recipients of CMV-negative donors and in CMV-negative HIV patients, CMV-safe products are given for the whole transfusion period; in neonates, until the age of 4 months; and in pregnant women, until delivery.

Question 3
Donor testing is performed by a commercial chemiluminescent immunoassay.

We are not currently contemplating implementation of nucleic acid testing for CMV, as implementation of new tests depends on appropriate ministry decision.

Although we cannot exclude inaccurate or incomplete reporting, we have not received any notification of TT-CMV since the implementation of the current policy.

In our centre, only repeat group O donors are tested for CMV: 1327 (39%) out of 3381 donors tested were found to be sero-negative.

In agreement with our policy (main use of leukoreduction), we maintain a very small inventory of 0-negative and 0-positive units, as the use of sero-negative donors is limited to a very small fraction of sero-negative patients. This is not a significant challenge.

Question 4
For RBC, leukoreduction used to mitigate the risk of CMV transmission is mainly done at the bedside (virtually all units are <8 days old); for newborns and for intrauterine transfusions, RBC units are filtered and divided into aliquots for repeat use in the same patient. All PLTs are prepared from buffy coats and filtered prestorage.

All leukoreduced units for the purpose of both prevention of febrile non-haemolytic transfusion reactions and CMV transmission must show a white cell count below $1 \times 10^6$ per unit. This is prescribed by the Italian blood transfusion law.

Question 5
In our opinion, serological screening for CMV can be abandoned if leucoreduction for components is applied.

We do not expect that local clinicians would oppose a policy of universal leucoreduction or pathogen reduction alone to prevent CMV

Question 6
Although consensus on the best policy for the prevention of TT-CMV is not universal, we believe that conclusive studies in this area would be extremely expensive and require significant efforts. Perhaps some resources could be used to improve our current systems of haemovigilance.

References
1 Bowden RA, Slichter SJ, Sayers M, et al.: A comparison of filtered leucocyte-reduced and cytomegalovirus (CMV) seronegative blood products for the prevention of transfusion


E. Raspollini, S. Villa & P. Rebulla
Centro trasfusionale e di Immunoonematologia
Fondazione Ca’ Granda Ospedale Maggiore Policlinico
Via Francesco Sforza, 35
20122 Milano
Italy
Email: e.raspollini@policlinico.mi.it

P. Rebulla
Center of Transfusion Medicine, Cellular Therapy and Cryobiology
Fondazione Ca’ Granda Ospedale Maggiore Policlinico
Via Francesco Sforza, 35
20122 Milano
Italy
Email: prebulla@policlinico.mi.it

P. Flanagan

**Question 1**
New Zealand Blood Service (NZBS) revised its approach to prevention of transfusion-associated CMV infection during 2010. The change followed extensive consultation with clinicians. Currently, the policy is that patients considered at risk of acquiring post-transfusion CMV receive standard prestorage leucodepleted components unless the clinician responsible for the patient specifically requests CMV-negative components. The request must be approved by a transfusion medicine specialist prior to CMV-negative components being provided. The only exception relates to components specifically manufactured for neonatal or intrauterine use where the current component specification requires the component to be produced from donations that test negative for CMV antibody. The policy statement is available on the NZ website [1] and applies to all hospitals in the country.

Clinicians are responsible for requesting access to CMV-negative components. A standard form is used, and a ‘patient protocol’ is added to the patient record in e-Progesa when supply is approved. The process for implementing the new policy involved gaining permission from responsible clinicians for the removal of pre-existing individual patient protocols. Near-100% agreement to removal was obtained as part of this process, indicating that clinicians are following the policy and comfortable that CMV-safe components produced by prestorage leucodepletion provide an acceptable level of safety with regard to CMV. This view is further supported by the fact that only nine patients have had protocols put in place during the last 2 years since the new policy was implemented.

There are currently no plans to implement pathogen reduction technologies in New Zealand.

**Question 2**
Patients at particular risk of acquiring transfusion-associated CMV include allogeneic CMV-sero-negative solid organ and haemopoietic progenitor cell transplant recipients where the donor is also CMV antibody negative, CMV-antibody-negative pregnant women, low-weight premature neonates and fetuses undergoing intrauterine transfusion. Systems for routine monitoring of transplant recipients for evidence of CMV infection have improved significantly in recent years allowing early initiation of specific antiviral therapy. This has reduced the morbidity and mortality of CMV in the transplant setting significantly. Given this, and the evidence of effectiveness of prestorage leucodepletion in reducing the risk of transmission, haematologists and transplant physicians involved in the consultation process used to establish the new policy identified that CMV-negative components would now only be required in exceptional cases using the approach identified above.

CMV-negative components continue to be provided for intrauterine and neonatal use. The requirement is linked with the component specification rather than the individual patient. These patients will therefore continue to receive CMV-negative components whenever a specific neonatal component is requested for a patient.

**Question 3**
The CMV-negative status of donors and donations is determined by the use of CMV antibody testing. Antibody testing is undertaken using the Architect CMV IgG assay (Abbott). There are currently no plans to extend testing to include detection of the virus by nucleic acid testing. Fifty-one per cent of previously untested donors are identified as CMV antibody negative. No problems are encountered in maintaining an inventory of CMV-negative components given their limited use.

No current data on the frequency of CMV transmission by transfusion is available.

**Question 4**
NZBS undertakes universal prestorage leucodepletion. The definition of leucodepletion is that ‘there is >95% confidence that >99% of components will have <5 × 10⁶ leukocytes’. Compliance is monitored using statistical process
control methods. No additional requirements are required to define the component as CMV safe.

**Question 5**

The current NZBS policy was developed in close consultation with clinicians responsible for the care of patients at increased risk in the event that they develop CMV disease. Improved early diagnostic tests and access to specific antiviral therapy have resulted in a significant reduction in morbidity and mortality. Clinicians in New Zealand are therefore generally comfortable that the level of protection afforded by prestorage leucodepletion is acceptable for most patients. Neither CMV testing nor prestorage leucodepletion will be 100% effective in preventing transfusion transmission. There is no evidence that the combination approach will increase the level of safety, and indeed, early data from Germany indicate that in fact the opposite might be the case and that the safest components with respect to CMV might be prestorage leucodepleted components derived from donors with a history of CMV infection of more than 1 year [2].

**References**

1. NZBS Policy on the provision of CMV antibody negative blood components. Available at: http://www.nzblood.co.nz/clinical-information/transfusion-medicine/clinical-compendium/clinical-policies-and-procedures/#.UzMGy2crjIU

P. Flanagan
New Zealand Blood Service
Auckland Mail Centre
Private Bag 92071
Auckland
1142 New Zealand
Email: peter.flanagan@nzblood.co.nz

D. Teo, S. Lam & A. L. Ang

**Question 1**

Where prevention of post-transfusion CMV is indicated, the practice is to use cellular blood components that are leucocyte-reduced by filtration. Screening of blood donations for CMV infection is not carried out in Singapore due to the relatively high prevalence of CMV-sero-positive blood donors.

Published national guidelines are available. The clinical practice guidelines (CPG) on clinical blood transfusion was developed by the national blood service (HSA) and Ministry of Health (MOH) in collaboration with the Academy of Medicine and relevant specialist user groups (haematologists, anaesthetists, surgeons, obstetricians, nursing, etc) and issued in February 2011 to all licensed physicians and hospitals. The CPG states that leucodepleted blood products are recommended as a means of reducing CMV transmission and CMV disease in immunocompromised patients.

The HSA-MOH CPG are followed by all doctors in the country and used as the standard for medical practice in clinical transfusion medicine. The primary responsibility for ordering CMV-safe products lies with the attending physician, although doctors from the blood service will also advise on the use of CMV-safe blood products where there is clinical indication. In patients with previous records of transfusion with CMV-safe blood, the hospital transfusion laboratories may also alert the attending physician if current requests do not include CMV-safe products.

Although pathogen reduction technologies are currently being studied as a means of reducing infectious disease transmission risk, it has not been implemented for cellular components.

**Question 2**

The CPG recommends the use of leucodepleted blood products as a means of reducing CMV transmission and CMV disease in immunocompromised patients. Different medical disciplines in hospitals maintain local guidelines to specify the type of immunocompromised patients who are at risk and therefore require CMV-safe blood products.

In general, most physicians follow the guidance from the blood service, which advises that CMV-sero-negative recipients at risk of CMV transmission via transfusion include the following:

- Patients undergoing bone marrow and stem cell transplants
- Premature infants and/or infants weighing <1200 g at birth
- Pregnant patients.

The duration that CMV-safe blood products are requested for and supplied in the populations below is as follows:

- Stem cell transplants – generally for life after an allogeneic stem cell transplant
- Neonates – generally for the duration of hospitalization.

**Question 3**

Blood donors are currently not tested for CMV. There is no plan at the moment to implement nucleic acid testing for CMV.

Previous studies in blood donors demonstrated a prevalence of 95% positive for CMV antibody. The national
haemovigilance programme has not reported any instances of CMV transmission since 2005. As seroprevalence of CMV in the adult population is high, it is also difficult to differentiate CMV reactivation from CMV transfusion through transfusion.

**Question 4**
Practically, all leucoreduced red cells are prepared at the blood service. The majority are prepared prestorage, although a small number is also prepared post-storage before issue. Use of bedside leucocyte filters for red cells has decreased over the years and are is uncommon.

Previously, only apheresis platelets were leucoreduced, and bedside filters had to be used for platelets prepared from whole-blood donors. However, since early 2012, all whole-blood-derived platelets supplied by the blood service are leucoreduced and the use of bedside leucocyte filters is correspondingly unnecessary.

The acceptable level, in terms of white blood cells per unit, which renders components 'CMV safe', has been defined as a residual leucocyte count of $5 \times 10^6$ and is based on the current AABB Standards.

**Question 5**
Current methods of leucoreduction reduce but do not completely eliminate white cells from the unit and hence will still carry some risk of CMV infection albeit much lowered. Similarly, the effectiveness of currently available pathogen reduction technology depends on the starting levels of pathogen present and will not be effective with high pathogen loads.

Whether to abandon serological screening for universal leucoreduction or pathogen reduction alone will therefore depend on a risk assessment taking into consideration population (donor and patient) prevalence. As CMV screening of blood donors is not carried out in Singapore, future strategies may instead focus on whether the addition of pathogen reduction processes to existing leucoreduction will result in improved safety.

D. Teo, S. Lam & A. L. Ang
Blood Services Group
Health Sciences Authority
Singapore
Email: Diana_TEO@hsa.gov.sg

M. Lozano, S. Sauleda, J. Cid & A. Perreira

**Question 1**
Currently in Spain, prestorage, universal leukoreduction of all the blood components is performed by vast majority of blood centres. In addition, some blood centres test donors using serology for CMV status.

There are no published national guidelines, so there are differences in practice between different autonomous regions and even between centres.

The clinicians are responsible for ordering CMV-seronegative products, although in our hospital, since we only use CMV-negative components for premature infants, we check with the neonatology ward the weight of the neonates when we receive a request for transfusion.

We have not implemented, or consider implementing, other measures.

**Question 2**
In our centre, we consider premature neonates (weight < 1500 g) as a high-risk population, and in addition to leukoreduced products, we provide them CMV-negative blood components. The reason for this being that after implementing universal leukoreduction in Catalonia in 2002, in the following years, we had three well-documented cases of transfusion transmission of CMV infection by leukoreduced red blood cell concentrates, which led us to add CMV-sero-negative donations to the leukoreduction.

Currently, there is a prospective cohort study ongoing in Atlanta to evaluate whether this double strategy (CMV-negative plus leukoreduced blood components) improves the outcome in low-birthweight infants (< 1500 g) born to both CMV-sero-negative and CMV-sero-positive mothers [1]. This policy is strictly followed.

Since all the blood components are leukoreduced in Catalonia, other patient populations with risk of significant morbidity and mortality after transfusion-transmitted CMV infection, such as CMV-negative recipients of allogeneic haemopoietic stem cell transplantation from CMV-negative donors, receive always CMV-safe products. A recent report suggests that that group of patients can be safely transfused with leukoreduced products. All the 23 CMV-negative patients receiving CMV-negative grafts and who received 1847 blood components from 3180 donors, remained CMV DNA negative, and none developed CMV-associated clinical complications. Interestingly, 17 of 23 patients seroconverted for anti-CMV IgG, but none for anti-CMV IgM; seroconverters received more transfusion per week that non-converters and the authors attributed anti-CMV IgG seroconversion possibly to passive antibody transmission by blood components [2].

- Currently, we do not think that our policy should be changed.
- Since prestorage, universal leukoreduction of all the blood components is the standard practice in the
Blood and Tissue Bank of Catalonia, all the patients receive CMV-safe products. The practice of providing CMV-sero-negative products to prematures weighing <1500 g is maintained, while the neonate needs transfusion support.

Question 3

• Blood donors are tested for the presence of CMV IgG and, if negative, for the presence of CMV IgM. If both markers test negative, the blood component is labelled as CMV negative.
• Although CMV nucleic acid testing should be a good complement to detect early CMV infection, we are not currently considering nucleic acid testing implementation because of difficulties in logistics and increase in costs.
• We do not have data on frequency of transfusion-transmitted CMV in our region. In the Catalonia Hemovigilance reports of 2009, 2010 and 2011, there are no cases of transfusion transmission of CMV.
• In our area, 70% of blood donors test CMV positive. In order to increase the yield of CMV-negative products, we select donors to be tested according to age and gender. Male donors below 33 years of age and female donors below 28 are selected for CMV screening. This strategy provides a CMV-negative yield of more than 50%.
• The Blood and Tissue Bank of Catalonia processes an average of 900–1000 donations per day to cover the blood supply in the region. This fact along with the previous strategy described to maximize CMV-negative yield is usually enough to produce the needed amount of CMV-negative platelets and to maintain adequate stock of CMV-negative red cells.

Question 4

• Leukoreduction is performed at the production stage in the Blood and Tissue Bank of Catalonia.
• According to the Guide to the Preparation, Use and Quality Assurance of Blood Components, the aim is to obtain <1 × 10^6 leucocytes per unit, deeming that the requirement is met if 90% of the units tested (1%) fall within the indicated values [3]. For reference, the mean content (±SD) in the third trimester of 2012 for red blood cell concentrates has been 0.27 ± 0.48 × 10^6 and for platelet concentrates 0.11 ± 0.13 × 10^6 (2012 16804 /id).

Question 5

• Probably in the future depending on the results of the ongoing studies, the serological screening of CMV might be abandoned if universal leukoreduction is in place, particularly at the levels of leukoreduction that the current filters can reach. The implementation of a pathogen inactivation technology would increase further the safety of the products, although nowadays, there are only technologies available for platelets and plasma [4].
• Clinicians in our institution probably would not oppose a policy of universal leukoreduction alone to prevent CMV transfusion transmission.

Question 3

• Additional studies are needed to better define the best strategy to prevent CMV transmission to populations with high risk of morbidity and mortality after transfusion transmission of CMV. Data available indicate that with our current strategies, we can significantly decrease the risk of transmission, but not completely eliminate such risk. Probably, only pathogen inactivation technologies will eliminate completely the risk of transmitting CMV by transfusion.

References


M. Lozano, J. Cid, A. Pereira
Department of Hemotherapy and Hemostasis
University Clinic Hospital
Villarroel 170
08017 Barcelona
Spain
Email: mlozano@clinic.ub.es

© 2013 International Society of Blood Transfusion
Vox Sanguinis (2013)
Question 1

- Which practice is currently used in your country/centre when prevention of post-transfusion CMV is indicated?

Leukodepletion. In a few centres also pathogen reduction technology for platelets – primarily introduced for the prevention of transfusion-transmitted bacterial infections.

- Are published national guidelines available or is the policy determined locally?

There are both national guidelines and locally determined policies.

- Are treating physicians following this policy?

Yes.

- Does the policy differ between types of facility (academic centre and community centre) or between different states/provinces/territories?

In a few centres, pathogen reduction technology is implemented for platelets, primarily, though for the prevention of transfusion-transmitted bacterial infections.

- Whose responsibility is it to order CMV-negative products: the transfusion medicine service or the clinicians?

The clinicians.

- Have you considered or implemented other methods to prevent post-transfusion CMV such as pathogen reduction technologies?

In a few centres, pathogen reduction technology has been implemented for platelets, primarily for the prevention of transfusion-transmitted bacterial infections.

Question 2

- For which patient groups is prevention of post-transfusion CMV essential? Are the criteria for these groups strictly followed?

Intrauterine transfusions, pregnant women, allogeneic (and autologous) haemopoietic stem cell transplantations, organ transplantations, neonatal transfusions, immunosuppressed patients. The criteria are strictly followed. In Sweden, most centres have introduced 100% leukodepletion of all blood products, that is, in these centres, there is no need to specifically order CMV-safe products. In 2011, around 90% of all red cell concentrates and 100% of all platelet concentrates in Sweden were leukodepleted.

- Do you think that your policy related to the use of CMV-safe products should be changed for certain populations? If so, which and why?

No.

- What is the duration that CMV-safe products are supplied in these special populations?

At one centre that does not leukodeplete all blood products, neonates up to 4 months of age are prioritized to receive CMV-safe products. Otherwise the duration that CMV-safe products are supplied for the mentioned special populations is forever.

Question 3

- How are blood donors tested?

In three centres, apheresis donors are tested by serology for anti-CMV, in case there is a need for granulocyte concentrates from these donors for transfusion to CMV-negative patients.

- Is your centre contemplating the implementation of nucleic acid testing for CMV?

No.

- What is the frequency of transfusion-transmitted CMV at your institution?

Don’t know, but there are no reported cases in the national haemovigilance system.

- If you are producing blood products, what per cent of your donor base is CMV negative?

Data from three centres are 20%, 37 and 41.8%.

- If your institution uses CMV-negative products, do you have challenges with maintaining an adequate inventory of CMV-negative products?

No. Except for granulocyte apheresis donations, CMV-safe/leukodepleted products is used.

Question 4

- When leukoreduction is used to mitigate the risk of CMV transmission, is it done at the bedside or at the production stage (prestorage)?
Prestorage.
• What is the acceptable level, in terms of white cells per unit, which renders components ‘CMV safe’?
  <1 million leucocytes per unit.

**Question 5**

• Do you think that serological screening for CMV can be abandoned when (universal) leukoreduction or pathogen reduction in blood products is applied?
  Yes.
• If you are in a jurisdiction that has options for both CMV-negative products and leukoreduced products, do you feel that clinicians working in your institution would oppose a policy of universal leukoreduction or pathogen reduction alone to prevent CMV?
  No. At one centre, they accepted the suggestion after discussion.

**Question 6**

• Do you think additional studies are needed to improve strategies for preventing of post-transfusion CMV? If yes, please indicate your suggestions (systematic review, consensus conference).
  Yes. One centre suggested a systematic review to be done and another centre that a consensus conference on the subject should be arranged.

B. Ekermo
Chair Working Group against Transfusion Transmitted Diseases
Department of Clinical Immunology and Transfusion Medicine
University Hospital
SE-58185
Linköping
Sweden
Email: Bengt.Ekermo@lio.se

C. Niederhauser, S. Waldvogel & S. Fontana

**Question 1**

Since 1 July 1999, all red cell, plasma or platelet processing methods must guarantee a leucocyte reduction to a level <10⁶ leucocytes per unit. This measure was made compulsory by the governing authorities in order to reduce the transmission risk of variant Creutzfeld–Jacob disease (vCJD) by transfusion. Furthermore, a nationwide pathogen reduction process of platelet products was implemented by the Blood Transfusion Service of the Swiss Red Cross beginning on 1 July 2011, using amotosalen hydrochloride and UVA irradiation (Intercept Blood System; Cerus Corporation, Concord, CA, USA). It has been reported by the manufacturer that this inactivation process reduces the level of CMV by up to 5–9 log. On the other hand, a consensus or directive to deal specifically with the prevention of CMV transmission by blood products has not be agreed upon, neither from the governing authorities nor from the Transfusion Services and nor from clinical or scientific organisations. For instance, it is not mandatory to test systematically for CMV in blood products; however, the National Swiss Transfusion Services regulations have laid out possible testing procedures. Therefore, every transfusion centre has implemented their own CMV policy, taking into account the local practices of physicians, of which many are quite diverse.

The introduction of universal leucocyte depletion procedure has led overall to a significant decrease in the demand of CMV-negative blood components. To date no transfusion-transmitted CMV infections (CMV-TTI) have been reported to the Swiss haemovigilance system. But because it is difficult to clearly identify a blood component transfusion as the origin of a CMV infection in risk patients, under-reporting is possible.

**Question 2**

The patients at high risk of severe morbidity related to CMV infection are allograft recipients, pregnant women and preterm infants. To our knowledge, there are at present no national Swiss guidelines dealing with potential transmission of CMV-TTI in these specific risk patients. In Switzerland, leucocyte reduction is mostly considered adequate for haemopoietic progenitor cells or solid organ transplant recipients. Possible exceptions include sero-negative recipients receiving a lung transplant from sero-positive donors, for whom, whenever possible, CMV-sero-negative products are ordered by some clinicians. In the last decade, universal leucocyte reduction has replaced the demand for CMV-sero-negative products. It seems that with this new strategy, the incidence of CMV infection/reactivation has not significantly increased, even though screening for viraemia has been performed more meticulously with the introduction of sensitive nucleic acid amplification techniques (NAT) in the post-transplantation follow-up. However, this expert judgment has not yet been supported by clinical trials.

Pregnant women may benefit from CMV-negative blood products, since systematic serological testing is not mandatory and recipient data are mostly not available. Intrauterine transfusions in some hospitals are systematically performed with CMV-sero-negative
products, making recruitment of blood donors more difficult.

**Question 3**
Systematic CMV testing is not at present routinely performed, but some blood transfusion centres perform such tests in special situations according to the specific requirements of the clinicians. In most cases, different anti-CMV assays are used; for instance, either an IgG assay alone or IgG in combination with a IgM assay. According to the National Transfusion Services regulations, labile blood products that are screened anti-CMV and tested negative are declared CMV sero-negative, whereas those testing positive are declared CMV sero-positive. There is no requirement to inform the donor on their CMV status. Only one of the regional Swiss Blood Transfusion Service (BTS) test routinely for anti-CMV (Enzygnost anti-CMV IgG/IgM, Siemens). Accordingly, nationwide epidemiological data for CMV prevalence in Swiss blood donors are currently not available. The prevalence of CMV-sero-positive blood donors in the BTS, which screens systematically for CMV, lies around 45% (90% repeat donors with an average age of 41 years).

**Question 4**
Universal prestorage leucocyte reduction has been mandatory by law since 1 July 1999. The regulations state that all red cell, plasma or platelet product processing methods must guarantee a leucocyte reduction down to $10^6$ leucocytes per unit (see Question 1). The framework of the processes and the quality control of these processes are described in the regulations and product specifications of the Swiss Blood Transfusion Services. The target of $<10^6$ leucocytes per unit is considered highly effective in preventing CMV-TTI, and several experts do not advocate the introduction of additional measures. On the other hand, the experts cannot agree to a consensus on what is an acceptable risk and which additional actions are required. This is particularly so for neonate or intrauterine transfusions.

**Question 5**
The present thought has put forward the policy that universal leucocyte reduction associated with pathogen reduction in platelets is sufficiently safe to defer the introduction of further mandatory CMV serologic tests of donors, even for neonates and intrauterine transfusions. Currently, there does not appear to be pressure to change these current policies.

We believe, however, there still exists a residual risk of CMV-TTI for susceptible patients with red cell transfusion, and thus, there is room for new studies, which in turn may lead to the introduction of new screening strategies to deal with this residual risk. The future policy in Switzerland is unlikely to be modified until such new data are available.

**Question 6**
The efficacy of leucocyte depletion on post-transfusion CMV infections is obvious. It would be, however, interesting to measure in a prospective clinical trial the remaining residual risk after this treatment. Such a trial would clearly require a large cohort, since the residual risk is certainly low. Moreover, the analyses may be hampered, since high-risk patients are often multitransfused and, to our knowledge, it is currently not possible to prove scientifically the causal relation between a transfusion-related and a reactivated CMV infection. CMV DNA analysis is probably more appropriate than serology to investigate these queries.

In intrauterine transfusions (IUTs), the selection of CMV-negative blood products has practical implications for recruitment of donors, especially in small centres. These products are rare since they must be carefully selected in order to prevent further alloimmunizations, and in addition, they are required to be fresh. These residual risk analyses and additional studies testing new screening or processing strategies need to be performed in order to determine the cost–benefit analysis of new procedures in comparison with the current CMV policy.

C. Niederhauser, S. Fontana
Blood Transfusion Service SRC Berne
Murtenstrasse 133
Berne
Switzerland
Email: christoph.niederhauser@bsd-be.ch,
stefano.fontana@bsd-be.ch

S. Waldvogel
Blood Transfusion Service SRC
Vaud
Epalinges
Switzerland
Email: Sophie.Waldvogel@mavietonsang.ch

M. J. Desborough & R. Pawson

**Question 1**
In the United Kingdom, universal leucodepletion of blood components has been used since 1998. The advisory committee on the Safety of Blood, Tissues and Organs (SaBTO) has recently published national guidance, which advocates the acceptance of CMV-safe, rather than CMV-negative blood components, for most patient groups [1]. There are
a number of exceptions, where CMV-negative blood is still recommended, which are dealt with in section 2. All cases of proven transfusion-transmitted CMV infection are required to be reported to national haemovigilance schemes: Serious Hazards of Transfusion (SHOT) and Serious Blood Reactions and Events (SABRE). The primary responsibility for ordering CMV-negative blood components is with the clinicians. There are no current UK-wide plans to introduce pathogen reduction technologies to further reduce the risk of CMV transmission.

**Question 2**
SaBTO considered that there was sufficient evidence of the equivalence of CMV-safe to CMV-negative blood components, that stem cell transplant/solid organ recipients and HIV-positive/immunosuppressed patients should receive CMV-safe blood components. However, it was felt there was insufficient clinical trial evidence to assess the safety of CMV-safe components for other populations, and CMV-negative blood components continue to be used for these patients.

Populations for whom transfusion of CMV-negative blood components continues to be recommended include the following: all women during pregnancy (although this is not necessary at delivery, it is emphasized that CMV-safe components should be used in emergency situations where CMV-negative components are not available), intrauterine transfusions and neonates (up to 28 days after delivery). The difficulty of diagnosing and treating CMV infection and the severity of its possible sequelae in intrauterine and neonatal infection were felt to justify a conservative approach. The use of CMV-negative blood components for granulocyte transfusions for CMV-negative recipients is also recommended due to the heavy lymphocyte and monocyte contamination of these components.

**Question 3**
60–75% of blood donors in the UK are CMV negative, and donors are not routinely tested for CMV. An enzyme immunoassay test (CMV IgG and IgM) is used when CMV-negative blood components are required. Nucleic acid testing has been considered, but is not currently recommended for screening blood donors, as there is variation in sensitivity and specificity between laboratories and a high rate of false-positive results [2]. However, nucleic acid tests are recommended for monitoring whether stem cell/solid organ transplant recipients have CMV reactivation.

No instances of transfusion-transmitted CMV have been reported to SHOT or SABRE, the haemovigilance schemes in the UK [3]. There are instances of neonates who received transfusions becoming CMV positive, but there is insufficient evidence to demonstrate a clear causal link.

Maintenance of adequate stocks of CMV-negative components can be challenging. Provision of CMV-negative red cells and platelets to the National Health Service (NHS) costs approximately £2.5 million per year, in addition to the costs of the blood components.

**Question 4**
Leucodepletion is applied preproduction within 24 h of collection with leucodepletion filters. The UK specification is \(<5 \times 10^6\) leucocytes per unit of platelets or red cells in 99% of components with 95% statistical confidence, and \(<1 \times 10^6\) leucocytes per unit in 90% of components. The cut-off of \(<5 \times 10^6\) leucocytes per unit (3 log depletion) is generally accepted as the level at which blood components are CMV safe [4].

**Question 5**
SaBTO felt that there was sufficient evidence that universal leucodepletion renders serological screening for CMV unnecessary in many circumstances. However, they felt that evidence was lacking in some patient groups (see question 2), and they should continue to receive CMV-negative components.

Neonatologists and obstetricians still advocate the use of CMV-negative blood, and there may be other isolated clinicians who would like to retain the right to use CMV-negative blood components in other groups of patients. If the use of CMV-safe components proves to be acceptable in other patient groups, this may provide clinicians with the confidence to extend its use to groups of patients who are still receiving CMV-negative blood components at present.

**Question 6**
No cases of (proven) transfusion-transmitted CMV have been reported to SHOT or SABRE in the UK within the last 10 years. However, now that transfusion policy has been changed to use CMV-safe, rather than CMV-negative blood, monitoring of haemovigilance data to ensure that any increase in transfusion-transmitted CMV across the population is detected and acted upon rapidly is essential.

We suspect demonstration that there is no increase in CMV infections when CMV-safe, rather than CMV-negative, blood is used in solid organ/stem cell transplants will be most likely to change obstetric and neonatal practice by providing reassurance that this approach is safe.

The role of nucleic acid testing is being explored in other countries, but its role in preventing CMV transmission remains to be defined.

© 2013 International Society of Blood Transfusion

*Vox Sanguinis* (2013)
Question 1

- The practice of preventing post-transfusion CMV includes both CMV-negative and CMV-safe blood products. However, there is no nationwide established policy for selecting either one or both types of products; thus, practice varies greatly depending on the patient population, underlying disease, type of transplantation and physician experience/comfort level.
- Circular of information published jointly by AABB, the American Red Cross, America’s blood centres and the Armed Services Blood Program states the following:
  - For at-risk recipients, the risk of CMV transmission by cellular components can be reduced by transfusing CMV-sero-negative or leucocyte-depleted components.
  - There is just one published national guidelines from the CDC, Infectious Disease Society of America and American Society for Blood and Marrow Transplantation on ‘Preventing Opportunistic Infections After Hematopoietic Stem Cell Transplantation’.
  - This policy states that sero-negative HSCT recipients should receive sero-negative or leucocyte-depleted blood products for both allo- and autograft recipients.
- There is no solid organ transplantation practice guidelines regarding this topic.
- Policy is determined locally for most practitioners.
- Treating physicians do not follow this policy, and some still insist on providing only CMV-negative blood products to their patients.
- There are differences that exist on multiple levels, within academic and community setting.
- Typically, it is the clinicians who order CMV products, though some institutions have internal guidelines that negate the need to place special orders. In addition, some transfusion medicine service staff or physicians will prospectively review the request for CMV-negative products to ensure the appropriateness of that order by verifying the patient’s underlying condition, CMV status and, if a transplant candidate, the donor’s CMV status.
- The current practice at Blood Systems, Inc. is to provide 100% leucocyte-reduced cellular blood components. We also perform CMV serologic testing as to meet the demands of physicians who either insist on providing CMV-negative blood components or to those patients who are at the highest risk of developing TT-CMV (e.g. fetus and neonates, CMV-sero-negative transplant patients with sero-negative donors).
- The FDA has not approved any pathogen reduction technologies in the USA.

Question 2

- Haemopoietic stem cell transplant patients (ALLO and AUTO), solid organ transplant patients (heart, lung, liver, intestine, kidney), HIV-positive patients, fetus and newborns <1200 g.
- There is a lack of general practice guidelines/standards dealing with this issue for the above patient population.
- We do not have an established policy related to this issue given that we are a blood centre and not a transfusion service. However, we do provide 100% leucocyte-reduced cellular blood components as a measure to reduce the risk of TT-CMV. Our belief based on published evidence is that CMV-negative
and CMV-safe blood components are equally safe, though we do recognize the need to continue providing CMV-negative blood components that have also been leucocyte-reduced for those patients who are at the highest risk of developing TT-CMV. We are aware of a recent preliminary publication describing the potential benefit of using LR blood from donors who have been sero-positive for CMV for more than 1 year. We believe this suggestion has some merit, but do not plan to implement it until more data in support of safety and efficacy are available.

- Not applicable. We are a blood centre and not a transfusion service

**Question 3**
- Donors are selectively for the presence of anti-CMV IgM and IgG using Olympus PK CMV-PA system. This system is a passive particle agglutination test for the detection of total CMV antibodies
- No, our centre will not implement a nucleic acid testing for CMV.
- Not applicable. We are a blood centre and not a transfusion service. Reporting transfusion-transmitted infections is passive. Reports of TT-CMV infections to our organization have been extremely rare.
- Averaging the last 5 years of data (2007–2011), 40.5% of donors tested negative for CMV. We tested a total of 397,562 unique donors during this period, and 161,142 of those tested were negative for total CMV antibodies
- Yes, we do have difficulties providing CMV-negative products at times; this is most commonly associated with platelet products especially in patients who are refractory to random donor platelets.

**Question 4**
- Prestorage leukoreduction
- <5 × 10⁶

**Question 5**
- No, at this time, there is not enough evidence to fully support completely abandoning screening for CMV in blood donors even in the presence of universal leukoreduction.
- Yes, they would likely oppose.

**Question 6**
- Yes, I believe additional studies are needed. I would propose a prospective, randomized study similar to the one published in 1995 Blood Journal by Bowden et al. This study compared the rate of CMV viraemia and CMV infection/disease in stem cell transplant patients who received exclusively either CMV-safe or CMV-negative blood components. It is important to recapitulate this study because the method for leucocyte reduction is different now being mostly or exclusively performed by the blood collection facility prior to storage. Also, the efficiency of the filters may have been improved significantly. Lastly, the test methods have also improved, which could minimize including patients who already have CMV prior to randomization.

M. Li, H. Kamel, M. Busch
Blood Systems, Inc.
6210 E. Oak St.
Scottsdale
AZ, 85252 USA
Email: MLi@bloodsystems.org

L. Qu & D. Triulzi

**Question 1**
In the USA, the AABB and CAP (College of American Pathologists) set the standards for clinical transfusion practice. The current edition of AABB Standards for Blood Bank and Transfusion Services (AABB Standards, 28th edition, 2012) requires that ‘the blood bank or transfusion service shall have a policy regarding transfusion of cellular components selected or processed to reduce the risk of cytomegalovirus transmission’. Both CMV-negative and CMV-safe (leucocyte-reduced) blood components are considered efficacious in preventing transfusion-transmitted CMV (TT-CMV) [1]. There is no national policy; practice is determined locally and varies from region to region. Most facilities follow the text from AABB Standards and Technical Manual [1] for clinical practice recommendations. Although the clinician can request CMV-negative or CMV-safe blood components, the transfusion service predefined the indications for such components based on criteria such as diagnosis and age. Other methods to prevent TT-CMV such as pathogen reduction are not available in the USA.

**Question 2**
CMV-reduced risk products (either CMV negative or CMV safe) are used to prevent primary CMV infection for patients at risk of CMV disease, as opposed to the usually asymptomatic primary infection experienced by the majority of immunocompetent individuals in the general population. These patient populations include the follow-
ing, and the criterion is usually strictly followed by our
transfusion service:

- CMV-sero-negative neonates weighing <1200 g;
- Neonates <4 months of age (calculated from full term) admitted to our tertiary care referral children's hospital (to avoid missing those with undiagnosed congenital immunodeficiency);
- Intrauterine transfusion;
- Sero-negative pregnant women;
- Sero-negative allogeneic haemapoietic stem cell transplant (HSCT) recipients (if donor also CMV-sero-negative) or sero-negative candidates for allogeneic HSCT;
- Sero-negative recipients of a solid organ transplant from a sero-negative donor;
- CMV-sero-negative HSCT donors;
- CMV-sero-negative patients with immunodeficiency syndromes.

In most immunocompetent transfusion recipients, primary CMV infection has little or no clinical consequence. It is in the most immunocompromised hosts such as stem cell transplant recipients that significant CMV disease develops, most of which occurs from reactivation of preexisting virus rather than newly acquired transfusion-transmitted infection [2]. Therefore, the CMV status of the patient and donor plays a role in selecting blood products. Given the limited supply of CMV-negative products, some institutions (including the authors') provide CMV-negative (and leucocyte-reduced) units to HSCT CMV-sero-negative recipients of CMV-sero-negative donors. In HSCT patients, when either the recipient or the donor is CMV positive, CMV-safe blood products are provided. The data supporting the slight superiority of CMV-negative over CMV-safe blood products in HSCT patients are based on a secondary end-point in the largest RCT [3] and a literature review with meta-analysis by Vamvakas [4]. Vamvakas analysed a total of 829 recipients of CMV-sero-negative components in 11 studies and a total of 878 recipients of leucocyte-reduced components in 12 studies. Among HSCT recipients, the risk of CMV infection was 1.63% (11 of 674) for CMV-sero-negative components and 3.01% (21 of 697) for leukoreduced CMV-safe components. In three studies that directly compared the two, CMV-sero-negative components were associated with 58% reduction in risk when compared with leucocyte-reduced (CMV-safe) components [4]. It should be noted that in a subset of studies integrated in the meta-analysis, CMV-negative and leucocyte-reduced (CMV-safe) components were virtually equivalent to each other when compared with CMV-unscreened/non-leucocyte-reduced components. The reduction in risk of CMV infection was 93.1% for CMV-negative and 92.3% for leucocyte-reduced (CMV-safe) components [4]. Whether the small risk difference between CMV-sero-negative and CMV-safe components is clinically relevant remains controversial.

Although the 'belt and suspenders' approach of providing leukoreduced blood components and using only CMV-negative blood donors for high-risk HSCT patients make intuitive sense, there are no data supporting the benefits of such approach. A recent small study in Germany suggested that the risk of transfusion-transmitted CMV infection is low in the high-risk HSCT patients [23 CMV-negative donor–patient pairs] who received leukoreduced blood products not tested for CMV antibodies [5]. The 23 patients received 1847 transfused products from 3147 donors and no observed cases of TT-CMV (95% CIs for the risk of TT-CMV in that population: 0–14% per patient and 0–0.21% per donor exposure) [5].

Given the potential for lifelong immunosuppression associated with HSCT and possibility of relapse, providing CMV-reduced risk blood (CMV-safe) products indefinitely is the approach we use. We have similar policies for patients who received solid organ transplantation, given the fact that these patients receive leukoreduced (CMV-safe) blood components to prevent HLA alloimmunization.

**Question 3**

The CMV seroprevalence varies based on the population and the geographic area studied. It is generally believed that 50–80% of US blood donors are CMV seropositive.

Donors are tested by serology for CMV. Blood components from donors with negative serology are labelled as CMV sero-negative at the authors' institution. The donor base has about 50% CMV-sero-negative donors. The reported TT-CMV in the area hospitals covered by the blood centre is rare; thus, the frequency is unknown. Our blood centre is not currently contemplating the implementation of nucleic acid testing for CMV. Like many blood centres that provide CMV-negative blood products, we have challenges in meeting the demand for such blood components, especially platelet components.

**Question 4**

Leukoreduction is performed either at the blood centre during manufacture (apheresis platelets or apheresis RBC units), at the blood bank laboratory before storage for RBC units (prestorage) or just before issue for whole-blood-derived platelets requiring pooling (post-storage). AABB Standards for Blood Bank and Transfusion Services establishes the acceptable level of white cells in leukoreduced blood components transfused in the USA. The 28th edition (2012) requires that leucocyte-reduced blood
components contain \(<5 \times 10^6\) leucocytes for apheresis platelets or RBC units and \(<8.3 \times 10^5\) for whole-blood-derived platelets in 95% of units sampled. The use of leukoreduction filters during the product preparation, not bedside filter, has been demonstrated to be consistently effective for providing CMV-safe products.

**Question 5**

Since the goal of any CMV testing is to identify potentially infectious donors, serological testing is not an optimal method since the transfusion of blood components from window-period donation presents the highest risk of TT-CMV infection. Ziemann et al. found that CMV plasma viraemia (non-cell-bound CMV DNA – a marker for free virus) was detectable in 44% of recently seroconverted blood donors and 3% of sero-negative window-period donation, whereas donors who were CMV sero-positive for 1 year or longer were not found to have measurable plasma CMV DNA [6]. Therefore, selection of CMV-sero-negative blood products could in fact paradoxically increase the probability of patients receiving a window-period donation compared to components from donors with long-term seroconversion (>1 year). We suggest that blood centres continue to perform CMV testing of donors and track those at least one year from first documented seroconversion and identify those leukoreduced components as CMV safe.

As such, we do not support abandoning CMV donor testing.

**Question 6**

Limited data suggested that leucocyte-reduced (CMV-safe) blood components are efficacious to prevent TT-CMV even for highest at-risk patient population [5]. Data are needed to show that the use of stable seroconverted donors has a rate of breakthrough that is equal to or less than the use of CMV-sero-negative blood donors. The low rate of TT-CMV infection and disease means that it is probably not practical to perform such as study. The ultimate solution to this issue will be pathogen inactivation of blood components, which will obviate the need for donor CMV testing.

**References**


L. Qu & D. Triulzi
Division of Transfusion Medicine
Department of Pathology
University of Pittsburgh & The Institute for Transfusion Medicine
3636, Boulevard of the Allies
Pittsburgh
PA, USA
Emails: lqu@itxm.org; dtriulzi@itxm.org

© 2013 International Society of Blood Transfusion
*Vox Sanguinis* (2013)