SaBTO

Advisory Committee on the Safety of Blood, Tissues and Organs

CYTOMEGALOVIRUS TESTED BLOOD COMPONENTS

POSITION STATEMENT

ISSUE

For a number of years, the literature has reported debate on the relative merit of providing cytomegalovirus (CMV) seronegative blood components versus leucodepleted components. There has been only one randomised trial (Bowden *et al*, 1995), and a number of non-randomised trials, which were all included in a meta-analysis of the results (Vamvakas, 2005;Drew & Roback, 2007). Leucodepletion has been in routine use for all blood components in the UK since 1999, and some countries do not test the CMV serostatus of leucodepleted components for certain at-risk patient groups.

SaBTO considered whether there was sufficient evidence to support the replacement of CMV seronegative cellular blood components (both red cells and platelets) with leucodepleted blood components. The potential risk to individual patient groups was considered, due to the possibility of more severe outcomes in some groups.

BACKGROUND

Cytomegalovirus

Cytomegalovirus is a herpes virus that gives rise to chronic, persistent and, for the most part, asymptomatic infection in a majority of adults worldwide. More severe disease may occur in certain groups, such as foetuses, neonates and immunocompromised adults. Following primary infection the host seroconverts, and CMV specific immunoglobulin G (IgG) persists lifelong together with cellular immune responses. A CMV seropositive individual is thus both *infected* and potentially *infectious* for life.

Lifelong infection and reactivation facilitates transmission to intimate contacts. CMV may be transmitted horizontally in saliva and other body fluids, blood, haemopoietic stem cells and organ transplants. In the UK 50-60% of adults are CMV seropositive, with an estimated seroconversion rate of 1% per annum. Vertical transmission with postnatal infection through breastfeeding is an important route of transmission. Congenital infection also occurs, especially with primary maternal infection in pregnancy, and is not uncommon, with rates of 0.3% of live births in the UK compared with 1% of live births in the USA.

Early detection of CMV infection is now possible, and treatment of CMV infection has improved and is more effective than previously.

Transmission of CMV by blood components

Transmission of CMV present in blood components can give rise to primary infection in CMV naïve recipients (transfusion-transmitted CMV) or to reinfection in previously infected individuals. The risk of transmission in multiply-transfused CMV negative recipients was greatly reduced by the provision of leucodepleted and/or CMV seronegative blood products (Drew 2007). Although this significantly reduces the risk of CMV transmission it is not 100% effective, with an estimated risk of 1.5-3.0% per recipient in the setting of bone marrow transplant (Vamvakas, 2005). CMV can be transmitted from blood donors with active (primary/reactivated) or latent infection. CMV may be present in circulating monocytes, or free in plasma as a result of primary infection or perhaps reactivation. The viral load is important, but the level in blood that will cause infection is not known.

Leucodepletion

Universal leucodepletion was implemented by all four UK Blood Services in 1999, primarily as a vCJD risk reduction measure. The UK specification for leucodepletion of $< 5 \times 10^6$ white cells per unit (3 log depletion, of 99% of components, with 95% confidence) is generally accepted as the level which renders components “CMV safe” (Vamvakas, 2005;Lipson *et al*, 2001;Drew & Roback, 2007).

CMV is thought to be latent in monocytes in the carrier (Taylor-Wiedeman *et al*, 1991) and there is evidence to suggest that leucodepletion filters are particularly efficient at removal of monocytes and could reduce CMV to no more than 0.1 viral copies per mL in leucodepleted blood (Pennington *et al*, 2001). Leucodepletion does not completely eliminate the risk of CMV transmission; there is a small risk that CMV could be transmitted in blood components of recently infected donors, due to the presence of virus in the plasma or the remaining white cell fraction.

The efficacy of leucodepletion is monitored by testing a proportion of components using flow cytometry and statistical process control. The chance of an issued component having a leucocyte count above the specification

(corrected residual risk, CRR) can be calculated. Data provided by NHS Blood and Transplant (Personal Communication from Sheila MacLennan) show that apheresis platelets had a CRR of 1:1403, pooled platelets of 1:354, and red cells 1:4278. Gross failures (> 100 x 10^6 per unit) only occurred during platelet apheresis, and are usually detected by the collection machine or noticed during visual inspection - these units are marked for leucocyte counting and discarded if non-compliant. Units with > 5 but < 100 x 10^6 leucocytes tend to be only just above the 5 x 10^6 per unit level, particularly for red cells.

Serological testing

A proportion of donations are screened by the Blood Services for CMV antibody to provide a 'CMV negative' inventory of cellular components, which are provided to hospitals on request. Depending on age group, 25-40% of UK blood donors are CMV antibody positive.

Antibody screening is performed using validated enzyme immunoassay (EIA) tests. Assays in use in the Blood Services detect total CMV antibody (IgG and IgM) with a sensitivity of > 99.5% (equating to a 'failure' rate of < 1:200) and specificity between 98.1% and 99.3%. Thus there is a small risk that CMV may be transmitted by a CMV seronegative component.

Nucleic Acid Technology (NAT) testing

Variation in the sensitivity and specificity of CMV NAT testing has been associated with widely varying estimates of the frequency of detection of CMV DNA in blood donations (Larsson *et al*, 1998;Roback *et al*, 2003;Roback *et al*, 2001). International multisite studies have shown inter- and intra-laboratory variation (Pang *et al*, 2009;Wolff *et al*, 2009). This should be improved by the recent establishment of an International Standard by the National Institute for Biological Standards and Control. Currently the use of CMV NAT detection to minimise transmission to high risk recipients is likely to generate a high proportion of initial false positives (Stramer *et al*, 2011).

MODELLING OF THE RISK OF CMV TRANSMISSION BY LEUCODEPLETED COMPONENTS

Statistical analysis was performed to assess the proportion of leucodepleted components that, although currently labelled as CMV seronegative, may still transmit CMV, compared with the corresponding proportion of untested leucodepleted components. Donors were divided into four groups:

1. Those very recently infected, before developing antibodies;
2. Those in the subsequent phase of infection, following seroconversion and with CMV DNA present in plasma and white blood cells;
3. CMV seropositive individuals following clearance of CMV from plasma; and
4. CMV seronegative individuals who have not acquired infection.

For the purpose of the modelling, it was assumed that donations from the first three groups are “infectious” in that their blood/components may transmit CMV to a recipient. The modelling did not take into account factors such as the predominant contribution of one donor to a pooled platelet component, or that the group who are DNA negative and seronegative are not an homogeneous group - data were not available to carry out, for example, age or gender stratification.

The analysis suggested that removal of the test for CMV antibodies would result in an increase in the number of potentially CMV infectious units that would be issued, although the size of this effect is uncertain. The scenarios presented gave a range for this increase of 85 to 774 units out of an approximate total of 467,800 issued as CMV seronegative, with the assumed proportion of the donor population that seroconverts in a year being the most influential variable.

There is a residual risk of CMV transmission by leucodepleted components, due to the presence of plasma or the remaining white cell fraction. This risk applies in the 6-8 week antibody window period and continues for up to one year following seroconversion (Drew & Roback, 2007;Ziemann *et al*, 2010). Therefore consideration was given to the potential consequence of CMV infection in specific patient groups.

CONSIDERATION OF SPECIFIC PATIENT GROUPS

Intra-uterine transfusions and neonates

CMV is the commonest cause of congenital infection in the developed world, affecting 1-2% of infants worldwide, recently reviewed by (Luck & Sharland, 2009b), and 0.3-0.4% in the UK (Griffiths *et al*, 1991). Up to 20% of babies who acquire congenital CMV die, and CMV is estimated to cause up to 12% of all sensorineural hearing loss (Peckham *et al*, 1987), and 10% of cerebral palsy. Primary infection is more likely to cause symptomatic congenital CMV and long term sequelae than reactivation of infection. Primary infection may increase the risk of abortion, stillbirth and fetal hydrops. Severe multisystem disease may be present which is clinically similar to congenital rubella or toxoplasmosis. CMV hepatitis can lead to intrahepatic and extrahepatic bile duct destruction as well as haemochromatosis. CMV infection of the fetal brain causes microcephaly, and hydrocephalus is also a feature of congenital CMV infection. Eye involvement, with chorioretinitis, cataract and blindness, occurs in 10-20% of cases presenting in the neonatal period.

Mortality from symptomatic neonatal CMV infection is between 10% and 30%, although much higher if the baby is premature. Babies most likely to be given blood components are those born preterm or those who are sick, and concern has been expressed that these babies will be at increased risk of the effects of CMV infection (Luck & Sharland, 2009a).

Given the potential severity of the consequences of CMV infection in this patient group, and the difficulty in monitoring neonates for infection (preventing pre-emptive therapy), it was considered to be important that leucodepleted and CMV seronegative blood components should continue to be provided.

- **CMV sero-negative red cell and platelet components should be provided for intra-uterine transfusions and for neonates (ie up to 28 days post expected date of delivery).**

- **All small sized blood packs and other cellular blood components intended for neonates should be provided as CMV seronegative.**

Pregnant patients

As many as 50% of pregnant women in the UK are CMV seronegative, and primary CMV infection in pregnancy is associated with a 40% risk of transmission to the foetus (Stagno *et al*, 1986). Women who are already CMV seropositive can also transmit infection, in some cases following reinfection with a different strain of CMV (Boppana *et al*, 2001).

Following primary maternal infection in pregnancy, 18% of neonates have clinical manifestations at birth (Fowler *et al*, 1992). Some infants whose mothers had primary or recurrent CMV infection in pregnancy only present later, with 5-17% manifesting CMV sequelae including sensorineural hearing loss and developmental delay.

In a recently published systematic review of antenatal interventions for preventing transmission of CMV from mother to foetus and adverse outcomes in the congenitally-infected infant, the authors found no randomised controlled trials meeting the criteria for inclusion (McCarthy *et al*, 2011). This contrasts with the successful prevention of CMV infection/disease by routine or pre-emptive prophylactic strategies in the post-transplant setting. Therefore emphasis has been placed on the importance of avoiding CMV infection or reinfection during pregnancy.

A single prospective study regarding transfusion-acquired CMV infection in pregnant women (Preiksaitis *et al*, 1988) summarised by (Blajchman *et al*, 2001) documented no seroconversions among 162 CMV seronegative pregnant women transfused with a mean of 2.7 units of red cells. However, only 8 of the women were transfused prepartum.

Pregnant women rarely require transfusion during pregnancy, the most common indications being in women involved in accidents or with pre-existing haemoglobinopathies. The lack of data regarding risk of CMV reinfection among pregnant women with major thalassaemia has been raised in this context (Eleftheriou *et al*, 1998).

There is a high risk of congenital CMV infection following primary maternal infection, and of immediate or later sequelae in the foetus or neonate, and the difficulty of early diagnosis and treatment makes successful intervention unlikely. Therefore it would be prudent to continue to minimise this risk by the use of CMV seronegative leucodepleted blood components in pregnant women receiving elective transfusions. This only applies to transfusion during pregnancy, not for blood components required in association with labour and delivery.

As CMV seropositive women are at risk of reinfection and vertical transmission of the newly-acquired CMV strain, CMV negative blood components should be requested for all elective transfusions during pregnancy, regardless of maternal CMV serostatus. This will avoid the need to determine maternal CMV status.

- **CMV seronegative red cell and platelet components should be provided for elective transfusions during pregnancy (not during delivery).**

- **If, in an emergency situation, it is not possible to provide CMV negative blood products, leucodepleted products of unknown serostatus may be used.**

HIV and immunodeficient patients

No relevant literature was found regarding HIV and CMV. Due to the modes of HIV transmission, virtually all individuals with HIV infection also have CMV infection. With routine antenatal HIV testing in the UK, vertical transmission is now rare, and infants with HIV infection usually already have CMV infection. The mainstay of CMV infection management is control of HIV infection, and effective treatment is available for CMV disease.

- **No relevant literature was found that supported the use of CMV seronegative blood for immunodeficient patients.**

- **These patients should receive leucodepleted blood.**

Haemopoietic stem cell transplant patients – adults and paediatrics

For many years it has been standard practice that CMV seronegative recipients undergoing transplant from a CMV seronegative donor are supported with CMV screened seronegative blood and platelet transfusions. Several studies have endorsed the rationale of this approach with rates of transfusion-transmitted CMV below 5% using seronegative products versus 28-57% with unscreened blood products (Bowden *et al*, 1987;Bowden *et al*, 1986;Miller *et al*, 1991).

In 1995 a study based in Seattle (Bowden *et al*, 1995) was the first and only large prospective randomised trial comparing the efficacy of CMV seronegative blood and platelet support to the use of leucodepleted components using a bedside filter. The primary conclusion from this study was that these two methods were equivalent in mitigating transfusion-transmitted CMV. In the secondary analysis of all infections occurring from day 0 to 100 post transplant, although infection rates were similar, the probability of CMV disease in the leucodepleted arm was greater. However, the authors accepted that there were possible explanations for this, and the overall conclusion of the paper was that leucodepletion was an effective strategy to significantly reduce transfusion-transmitted CMV and screening/selection of seronegative components could be discontinued.

A non-randomised study from the same centre but with different authors (Nichols *et al*, 2003) looked at all CMV negative/negative transplants in two timed cohorts, and found that the use of filtered red cells from CMV positive donors was the primary predictor of transfusion-transmitted CMV. The use of Ganciclovir prevented all but one case of CMV disease, illustrating the importance of early CMV detection and effective treatment.

In a smaller non-randomised study (Ljungman *et al*, 2002), there was no significant difference in infection or disease in CMV negative patients receiving screened plus filtered blood products versus leucodepleted products alone. In two cohorts of patients reported from Bristol there was a zero incidence of CMV infection/disease both in patients receiving CMV seronegative blood and platelets (Foot *et al*, 1998) 110 allograft patients) and in those receiving CMV seronegative red cells plus non-screened leucodepleted platelets (Ronghe *et al*, 2002;Ronghe, 2008) 93 allograft patients). In these studies all patients and stem cell donors were seronegative and underwent regular CMV testing.

It should be noted that in Seattle, the largest transplant centre in the world, seronegative screened products have been abandoned in favour of pre-storage leucodepletion, although data on outcomes are lacking (James Aubuchon, personal communication).

In conclusion, rates of transfusion-transmitted CMV have been very low with both leucodepletion and serology screening, and the two techniques are probably equivalent. With both approaches there is likely to be a low failure rate.

CMV monitoring and early therapy may be a successful strategy for mitigating against any potential clinical effects. Indeed the routine use of CMV quantitative PCR monitoring and pre-emptive therapy in the setting of stem cell transplantation has significantly reduced the mortality from CMV infection overall (even in transplants involving seropositive recipients and/or donors). Monitoring and pre-emptive therapy is not currently universal practice for seronegative recipients of a seronegative haemopoietic stem cell transplant, but it is recommended that this should become standard practice in order to

allow early detection and treatment of infection, whether this is transfusion-transmitted or naturally acquired primary infection.

As many as 25% of haemopoetic stem cell transplants may be performed using CMV positive stem cell donors and CMV seronegative recipients (in the absence of an equivalent tissue matched seronegative donor), representing a significant risk of primary infection. Any transfusion-transmitted CMV should be viewed in this context. In addition, the mortality from other viral infections (eg respiratory viruses), bacterial and fungal infections far exceeds that of CMV in current transplant practice.

- **CMV seronegative red cells and platelets may be replaced with leucodepleted blood components for adults and children post haemopoeitic stem cell transplantation, for all patient groups including seronegative donor/seronegative recipients.**

- **Patients requiring transfusions who may require a transplant in the future may also safely be transfused with leucodepleted products (eg seronegative leukaemia or thalassaemia patients).**

- **CMV PCR monitoring should be considered for all patients (even CMV negative/negative patients) to allow early detection of any possible CMV infection (whether transfusion-transmitted or otherwise acquired).**

Organ transplant patients

i) Adult patients

Of all the solid organ transplants, the lung is the most seriously affected by CMV infection. This is a reflection of the high level of immunosuppression required, the vulnerability of the lung itself to the damaging effects of infection, and the transplanted organ's range of impairments to local defences. The lung can therefore be used as a bellweather for potential effects on other organs.

Concern centres entirely around organ donor-aquired infections. The viral load transmitted in the lung, which is rich in lymphoid tissue and a reservoir for monocytes, is significant. A recent international survey of management practices did not mention transfusion-acquired infection (Zuk *et al*, 2010).

Roughly half adult organ donors are CMV positive, as are half the recipients. Approximately 25% of recipients will be donor positive, recipient negative, and therefore at risk of primary, donor-aquired infection, at a time when immunosuppression is at its highest level. This used to be a major concern, but has almost disappeared in the era of effective viral prophylaxis (Mitsani *et al*, 2010;Manuel *et al*, 2009). The same applies even to children, traditionally the most vulnerable group (Danziger-Isakov *et al*, 2009).

None of these recent reviews mentions transfusion-acquired infection. Further evidence that it is of little concern is the very low incidence of seroconversion in negative recipients who receive organs from seronegative donors, and do not routinely receive CMV seronegative blood (John Dark, Personal Communication). They receive no prophylaxis, or even monitoring. The rate of seroconversion is regarded as significantly less than the 1% per year quoted for their non-transplant equivalents.

There are no published studies comparing leucodepletion with CMV screening for blood or blood components given to lung transplant recipients. Given the very low risks involved, it is unlikely that any study could differentiate transfusion- from community-acquired infection.

ii) Paediatric Patients

CMV has a relatively high incidence in patients receiving solid organ transplants, and is the most frequent infectious complication. The risk varies with the type of organ received; the highest to lowest risk are lung, small intestine, pancreas, kidney, liver and heart.

CMV positive organs are used in CMV negative patients due to their scarcity and the high risk of patients dying on the waiting list. Hence primary CMV infection is given to some recipients during solid organ transplantation. There is limited evidence of transfusion-transmitted CMV in the solid organ transplant population but routine monitoring of negative recipients of negative donors is not universal.

As noted above, the risk of primary, donor-acquired infection, at a time when immunosuppression is at its highest level, used to be a major concern. However, effective viral prophylaxis has alleviated this (Mitsani *et al*, 2010;Manuel *et al*, 2009) even in children, traditionally the most vulnerable group (Danziger-Isakov *et al*, 2009).

iii) Conclusion

There is no published evidence of transfusion-transmitted CMV infection that would support the use of CMV seronegative blood for transplant patients. Testing of recipients and monitoring of outcomes is needed to provide more data in this area. The European Union Organ Donation Directive comes into force in August 2012, and will require reporting of serious adverse events and adverse reactions, which may help with reporting.

- **Organ transplant patients do not need to receive seronegative blood and should receive leucodepleted blood.**

- **Individual units should consider whether or not a policy of CMV PCR monitoring for some groups of patients (even CMV negative/negative patients) should be introduced to allow early**

detection of any possible CMV infection (whether transfusion-transmitted or otherwise acquired).

Granulocyte components

Granulocyte components should continue to be provided as CMV seronegative for CMV seronegative patients. Granulocyte components can not be leucodepleted.

POTENTIAL IMPACT ON BLOOD SERVICES AND HOSPITALS

Supply and cost of CMV seronegative components

The number and proportion of CMV negative platelets and red cells has shown a gradual increase over the last five years and in 2009/10 amounted to 12% of red cells issues and 37% of platelets. NHS Blood and Transplant charges a supplement to cover the costs of screening and holding a separate inventory, leading to recovery of approximately £2.5 million per annum from hospitals. Reduced CMV testing will result in an immediate reduction in direct consumable costs as well as the potential, over time, to reduce other supply chain costs (a 2% reduction in wastage could save £0.3 million).

Advantages of a single inventory

Accepting leucodepleted components as CMV safe has advantages both for blood banks and blood establishments. Inventory management will be much less complex, and wastage is likely to be reduced. NHS Blood and Transplant estimates that approximately 50% of *ad hoc* deliveries to hospitals contain CMV seronegative platelets at a cost of approximately £0.1 million. Further, when the Belgian blood service implemented pathogen reduction of platelets (which inactivates CMV), platelet wastage fell by 1.5%. If the need to select for CMV negative platelets was removed, this could save £0.22 million. Blood components for neonatal transfusions are routinely supplied as smaller sized ‘split’ units, which are therefore easier to consider separately.

Other safety initiatives may be facilitated by removal of the need for a second inventory, and reduced wastage. The target of 80% platelets by apheresis could be met more easily and consistently; recruitment of more male platelet donors would assist with TRALI (transfusion related acute lung injury) risk reduction, and clinical errors (not supplying CMV seronegative components) may be reduced.

SUMMARY OF RECOMMENDATIONS

SaBTO has reviewed the evidence around the replacement of CMV seronegative cellular blood components (both red cells and platelets) with leucodepleted blood components. The following conclusions were reached:

1. CMV seronegative red cell and platelet components should be provided for intra-uterine transfusions and for neonates (ie up to 28 days post expected date of delivery), and therefore all small sized blood packs and other cellular blood components intended for neonates should be provided as CMV seronegative.

2. Granulocyte components should continue to be provided as CMV seronegative for CMV seronegative patients.

3. CMV seronegative blood components should be provided where possible for pregnant women, regardless of their CMV serostatus, who require repeat elective transfusions during the course of pregnancy (not labour and delivery). This mainly applies to patients with haemoglobinopathies who are managed in specialist centres. However CMV seronegative blood components are not expected to be generally available in all hospitals and therefore for emergency transfusions in pregnant women, leucodepleted components are recommended.

4. All blood components (other than granulocytes) in the UK now undergo leucodepletion, which provides a significant degree of CMV risk reduction. This measure is considered adequate risk reduction for all other patients requiring transfusion (haemopoetic stem cell transplant patients, organ transplant patients, and immune deficient patients, including those with HIV) without the requirement for CMV seronegative components in addition.

5. CMV PCR monitoring should be considered for all haemopoeitic stem cell and solid organ transplant patients (even CMV negative donor/negative recipients) to allow early detection of any possible CMV infection (whether transfusion-transmitted or primary acquired infection).

6. Transfusion-transmitted CMV infections should be reported via the SHOT (Serious Hazards of Transfusion) and SABRE (Serious Adverse Blood Reactions & Events) systems.

The report of the SaBTO CMV Steering Group may be found at:

www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_132965

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