CLINICAL GUIDELINES FOR THE PROVISION OF CMV SERONEGATIVE BLOOD COMPONENTS

Executive Summary

The following document details the purpose, methodology and clinical consensus statements that have been developed by the Blood Service on behalf of the NBA regarding the clinical indications for CMV seronegative blood components and their priority in a time of supply shortage.

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Introduction

A proportion of donations are screened by the Australian Red Cross Blood Service (Blood Service) for cytomegalovirus (CMV) antibody to provide a CMV seronegative inventory of cellular blood components, which are provided to hospitals on request. A significant proportion of the donor population are CMV seropositive with the proportion increasing with increasing donor age. For this reason, at times, there may be shortages of CMV seronegative blood components, and in particular of CMV seronegative platelets.

CMV is thought to be latent in monocytes and there is evidence to suggest that leucodepletion is particularly efficient at the removal of monocytes and significantly reduces the risk of transfusion-transmitted CMV infection. For a number of years, the literature has reported debate on the relative merit of providing CMV seronegative blood components versus leucodepleted blood components. However, neither the provision of CMV seronegative blood components nor the provision of leucodepleted blood components completely eliminates the risk of CMV transmission. The Blood Service introduced universal leucodepletion of red cells and platelets in October 2008.

The purpose of this document is to seek and achieve consensus with regards to the indications for the provision of CMV seronegative blood components, including which patient categories should receive priority for the supply of such components during periods of supply constraints. The recommendations included in this document take into consideration the position statement on CMV tested blood components prepared by the UK Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO), a review of recent literature, the results of a recent survey of current clinical practice regarding the prescription of CMV seronegative blood components in Australian hospitals and expert consensus.

The outcomes from this process will also guide the development of an annex for the National Blood Supply Contingency Plan (NBSCP). The NBSCP was developed by the National Blood Authority (NBA) to facilitate and coordinate a rapid national response in the event of a domestic threat or disaster that affects the provision of a safe and adequate blood supply in Australia. It outlines the crisis planning, preparation and mitigation of a crisis, response framework and recovery arrangements for a crisis affecting the supply of blood and blood products. It also provides guidance on the escalation of contingency management from NBSCP arrangements to the Australian Health Protection Principal Committee (AHPPC). As part of this framework the NBA has prepared NBSCP Annex C – Platelets to support the response to a range of risks identified for platelet supply including the prioritisation of requests for CMV seronegative blood components during periods when supply is constrained

The document is presented in three sections as follows:

- Part A: Background information
- Part B: Clinical indications for CMV seronegative blood components
- Part C: Prioritisation of CMV seronegative blood components

Part A: Background Information

Consensus Methodology

Criteria for establishing the consensus group:

As part of the NBA Platelets Project deliverables, the Blood Service was required to assemble a group of external expert clinicians to assist with the development of consensus statements incorporating clinical indications and prioritisation for the provision of CMV seronegative platelets. This was subsequently extended to incorporate all blood components.

The Blood Service external Advisory Committee members were engaged as the consensus group members for this process. In addition, a Consultant Haematologist with paediatric and obstetric expertise was targeted to ensure broad clinical representation within the group. Final membership included representation from clinical and laboratory haematology, transfusion medicine, intensive care, microbiology, infectious diseases, molecular genetics, transplantation, research, anaesthetics, orthopaedics and oncology. A representative from the NBA was also included in the consensus group as an observer of the process.

As part of the selection process, consensus group members had to be able to commit themselves to the consensus process and timelines for the project.

Drafting of the consensus statements:

The recommendations included in this document take into consideration the position statement on CMV tested blood components prepared by the UK Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO), a review of recent literature, the results of a recent survey of current clinical practice regarding the prescription of CMV seronegative blood components in Australian hospitals and expert consensus. A targeted literature search was also conducted in order to develop the background paper and 4 associated consensus statements.

The consensus statements and supporting information were initially reviewed by the Blood Service National Blood Transfusion Committee. Membership of this committee includes internal and external haematology and transfusion medicine experts. A subsequent review and final approval was conducted by Blood Service personnel with laboratory and clinical haematology expertise prior to being disseminated to the consensus group members for consideration.

Key literature review

Ziemann et al (*Window period donations during primary cytomegalovirus infection and risk of transfusion-transmitted infections.* Transfusion 2013; 53(5): 1088–1094) recently examined the frequency of CMV window period donations as a means of determining whether selection of seronegative donors might be advantageous for patients at risk of transfusion-transmitted CMV infections. The authors investigated 93 donors with positive results on routine CMV antibody testing within at most 35 days after their last seronegative sample. CMV seroconversion was evaluated on Western blot and/or a second antibody assay. CMV seroconversion was only confirmed in 12 of the 93 donors (13%). Of these, the last seronegative sample was CMV DNA positive in 3 donors (25%), all with DNA concentrations below 30 IU/mL. The first seropositive sample was CMV DNA positive in 10 donors (83%) with a maximum DNA concentration of 1600 IU/mL. Both the prevalence and median concentrations of CMV DNA were higher in the first seropositive sample, with maximum concentrations being reached about 2 weeks after seroconversion. No CMV DNA was detected in samples from donors with unconfirmed seroconversion.

The authors concluded that “at least in donors with short interdonation intervals, most suspected CMV seroconversions are due to false-positive results of the screening test. As window period donations are rare and contain less CMV DNA than the first seropositive donation, avoidance of blood products from primarily

seropositive donors is especially helpful to avoid TT-CMV if donors with short interdonation intervals are concerned."

A more recent article also by Ziemann et al (*The impact of donor cytomegalovirus DNA on transfusion strategies for at-risk patients.* Transfusion 2013). Article first published online: 14 April 2013. doi:10.1111/trf.12199) discusses the impact of donor CMV DNA on transfusion strategies for at-risk patients. The authors found that the "prevalences of window period donations among seronegative donors and reactivations among long-term seropositive donors, as well as the CMV DNA concentration in whole blood and plasma samples from these donors, are comparable". They concluded that blood components from both seronegative and long-term seropositive donors could be used for patients at risk for transfusion-transmitted CMV and that newly seropositive donors posed the greatest risk.

UK Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO), Cytomegalovirus Tested Blood Components, Position statement

In March 2012, SaBTO published a position statement on the provision of leucodepleted and/or CMV seronegative blood components to reduce the risk of transmitting CMV via transfusion. SaBTO reviewed the evidence and considered whether it supports the replacement of CMV seronegative blood components (red cells and platelets) with blood components that have been leucodepleted but not CMV screened. SaBTO considered the potential risk to specific patient groups, given the possibility of more severe outcomes of infection in some groups, and concluded that the range of patients provided with CMV screened blood should be reduced. The position statement sets out the background, the relevant factors for each patient group, and SaBTO's conclusions and recommendations on the type of blood components suitable in each case. The statement notes that there has only been 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)*. The position statement is published at http://www.dh.gov.uk/health/2012/03/sabto/.

SaBTO recommends a more restricted list of clinical indications for CMV seronegative blood components compared with current Australian practice, as detailed in the table below.

Table 1: Comparison of ANZSBT/Blood Service guidelines vs. SaBTO Position Statement

Indication	ANZSBT / Blood Service	SaBTO
Intra-uterine transfusions	Yes[1]	Yes
Premature neonatal transfusions	Yes[1, 2]	Yes
Other neonatal transfusions (≤ 28 days post EDD)	Yes[1, 2]	
Granulocyte transfusions	Not specified	Yes
Immune deficient patients	Yes[3]	**No**
Autologous HSCT patients	Yes[4]	**No**
Allogeneic HSCT patients	Yes[4, 5]	**No**
Organ transplant patients	Yes[4]	**No**
Pregnant women	Yes[6, 7]	Yes

Notes

1. For transfusion of the fetus and neonate 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" [ANZSBT *Guidelines for pretransfusion laboratory practice*; 2007]
2. Premature (< 1500g) or immunocompromised neonate [Blood Service *Blood Component Information*; 2012]
3. CMV-seronegative recipients of highly immunosuppressive chemotherapy e.g., leukaemia, lymphoma [Blood Service *Blood Component Information*; 2012]
4. CMV-seronegative recipients of allogeneic or autologous stem cell, bone marrow or solid organ transplants [Blood Service *Blood Component Information*; 2012]
5. For recipients of allogeneic haemopoietic stem cell grafts all cellular components "should be CMV negative where indicated" [ANZSBT *Guidelines for pretransfusion laboratory practice*; 2007]
6. CMV-seronegative pregnant women who require transfusion [Blood Service *Blood Component Information*; 2012]
7. The use of "CMV-antibody negative or CMV safe (i.e. leucocyte depleted)" blood components "should be dictated by local or national policies" [ANZSBT *Guidelines for pretransfusion laboratory practice*; 2007]

Challenges with CMV testing

There are some challenges with CMV serological testing. The commercial CMV IgG assays employ viral lysate of laboratory adapted CMV AD169 strain as target, and it is known that this strain's genome contains several important deletions as compared to clinical strains. Therefore sera from individuals infected by some clinical strains may not show reactivity with these IgG assays. In addition there will be window period donations where despite the individual being infectious the IgG result will be negative.

Modelling the residual risk of CMV from CMV untested leucodepleted blood

The risk of CMV transfusion transmission is not easily estimated because of a number of key knowledge gaps including the minimum infectious dose in humans and the frequency and infectivity of cell-free CMV in plasma. The residual risk for leucodepletion is assumed to be the result of two limitations. Firstly the failure rate of leucodepletion filters ('filter failures') to remove white blood cells below the threshold of infectivity (i.e. 5×10^6 per component based on studies in mice) and secondly the inability of filters to remove cell-free CMV. Estimation of the first risk component may be possible using Blood Service process control data for residual white cell counts for leucodepleted components and the published data on the frequency of CMV DNA carriage. However defining the risk from cell-free virus in plasma is very challenging and may well not be possible with any degree of accuracy.

The Blood Service is currently undertaking modeling to derive residual risk estimates which will be submitted for publication in a peer-reviewed journal. Current estimates indicate that the residual risk for CMV transmission per CMV untested leucodepleted component transfused is very low.

Current Australian clinical practice

In September 2012, the Blood Service distributed a policy and practice survey to determine current clinical practices regarding the use of CMV seronegative blood components. The survey sought feedback from haematologists, specialists involved in solid organ transplantation, obstetrics and neonatal care, and scientists. There were a total of 123 respondents to the survey with all states and territories represented, as well as two responses from overseas. 60% of respondents identified themselves as clinicians, including haematologists, clinicians involved in solid organ transplantation and obstetricians. The remaining 40% of respondents were scientific or technical staff, with the majority being senior scientists.

The following is a summary of the main conclusions from the survey:

- The majority of respondents' hospitals have policies/guidelines for the use of CMV seronegative blood components which appear to be well adhered to by treating physicians
- Leucodepleted (LD) components are not considered equivalent to CMV seronegative blood components, however 58% of respondents would use LD components if CMV seronegative components were unavailable
- LD alone is not considered adequate enough to prevent CMV transmission
- Approximately 80% of respondents do not believe the Blood Service should cease serological screening for CMV
- CMV quantification to determine the presence of CMV is not common practice in the transplant setting
- Most clinicians do not order/request/use CMV seronegative components for patients where there is no indication for use
- Approximately two thirds of respondents indicated that they would issue CMV seronegative components to patients where these are not specifically indicated to avoid expiry
- In certain clinical situations, 65% of clinicians may possibly approve the issue of a CMV-untested blood component that was close to expiry to a CMV negative patient, compared to 65% of scientists who would never approve this process.

The findings of the survey, whilst they may not be statistically robust, do provide an insight into Australian attitudes around the clinical use of CMV seronegative blood components. The findings of the survey highlight that a significant proportion of health professionals currently do not believe that leucodepleted blood

components are equivalent to CMV seronegative components and clinicians still have a strong desire to prescribe CMV seronegative components across the full range of “at risk” patient groups. The use of CMV seronegative blood components was also a topic of the Blood Service Transfusion Update held in June 2013. Feedback obtained at this meeting from health professionals was strongly consistent with the feedback obtained in the survey and clinicians did not consider that there was sufficient evidence to justify a change in clinical practice at this stage.

Inventory management and cost implications

As noted in the SaBTO Statement, accepting leucodepleted components as CMV safe has advantages for hospitals, the Blood Service and governments. Inventory management would be much less complex, wastage is likely to be reduced and there would be cost savings arising from a reduction in the number of ad hoc deliveries to laboratories and the cost of testing.

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Part B: Clinical Indications for CMV Seronegative Blood Components

Consensus Statement 1 – Clinical indications for CMV seronegative blood components

CMV seronegative products may be an appropriate option in the following clinical indications:

- Intra-uterine transfusions and neonates
- All pregnant women regardless of CMV status having antenatal transfusion with ongoing pregnancy
- CMV seronegative recipients of allogeneic or autologous stem cell, bone marrow or solid organ transplants
- CMV seronegative recipients of highly immunosuppressive chemotherapy
- Granulocyte component therapy

The above indications are consistent with the information included in the current Australian Red Cross Blood Service Blood Component Information Booklet and the ANZSBT Guidelines for pretransfusion laboratory practice, 5th edition, March 2007 – Section 2.6.3.

Part C: Prioritisation of CMV Seronegative Blood Components

Supply constraints for CMV seronegative blood components may occur alone or in association with a general shortage of blood components. Within either of these scenarios, platelets are most commonly impacted because of their short shelf-life followed by Group O RhD negative red cells.

During periods where CMV seronegative blood component supply constraints occur in isolation, it may be necessary to prioritise supply of such components to patients with the greatest clinical need. In this scenario, all clinically appropriate requests for the supply of blood components are able to be met, albeit the supply of CMV seronegative blood components for some patients may be briefly delayed or may need to be met with CMV untested or CMV seropositive leucodepleted blood components. (Note: The Blood Service specifically labels components that test CMV seronegative. Components that test CMV seropositive are not labeled as such). Prioritisation of supply in this scenario is undertaken by medical staff at the Australian Red Cross Blood Service in consultation with the treating clinician.

However, where the supply constraint is more severe and is in association with a general shortage of blood components, it may be necessary to restrict the supply of blood components to particular patient categories. In these situations, the NBSCP will be activated and there will be communication between stakeholders, including the National Blood Authority (NBA), Jurisdictional Blood Committee (JBC), Australian Health Protection Principal Committee (AHPPC) and the Blood Service. Prescribing clinicians will be informed about the necessity to reduce the demands for blood components.

This document provides guidance for the prioritisation of the supply of CMV seronegative blood components during periods when activation of the NBSCP is required as well as during periods when activation is not required. In descending order of urgency, patients can be classified in CMV Seronegative Priority 1-3, patients classified in CMV Seronegative Priority 1 have the highest priority for transfusion of CMV seronegative blood components.

Consensus Statement 2 - CMV Seronegative Priority 1

During periods when supplies of CMV seronegative blood components are constrained, the following patients have the highest priority for transfusion of these blood components and are classified as “CMV Seronegative Priority 1”.

- Intra-uterine transfusions and neonates
- CMV seronegative pregnant women having antenatal transfusion with ongoing pregnancy

As noted in the SaBTO statement, CMV is the commonest cause of congenital infection in the developed world, affecting 1-2% of infants worldwide. Up to 20% of babies who acquire congenital CMV die, and CMV is estimated to cause up to 12% of all sensorineural hearing loss and 10% of cerebral palsy. Primary infection is more likely to cause symptomatic congenital CMV and long term sequelae than reactivation of infection. CMV infection of the fetal brain causes microcephaly and hydrocephalus. Eye involvement (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.

As noted in the SaBTO statement, primary CMV infection in pregnancy is associated with a 40% risk of transmission to the foetus. Following primary maternal infection in pregnancy, 18% of neonates have clinical manifestations at birth. In a recently published systematic review of antenatal interventions for preventing transmission of CMV from mother to foetus, the authors found no randomised controlled trials meeting the criteria for conclusion. 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 during pregnancy.

Consensus Statement 3 - CMV Seronegative Priority 2

During periods when supplies of CMV seronegative blood components are constrained, the following patients have moderate priority for transfusion of these blood components and are classified as "CMV Seronegative Priority 2".

- CMV seronegative recipients of allogeneic stem cell, bone marrow or solid organ transplants receiving a seronegative transplant
- CMV seronegative recipients of highly immunosuppressive chemotherapy

In the setting of organ donation there are three potential sources of infection – endogenous reactivation, the donor organ and cellular blood components; with the donor organ being the most important source. As noted in the SABTO review, in the era of effective viral prophylaxis (Mitsani et al, 2010; Manuel et al 2009), this risk has almost but disappeared. The reduction in risk is also seen in organ transplantation in children, traditionally the most vulnerable group (Danziger-Isakov et al 2009). Exposure to CMV seropositive blood in a seronegative patient receiving a CMV positive donation does not appear to increase risk of CMV related seroconversion or disease (Preikaitis et al 2002).

The only large prospective randomised trial comparing the efficacy of CMV seronegative blood components with leucocyte-depleted blood components for haemopoetic stem cell transplants was conducted by Bowden et al in 1995. It is important to note that this study used bedside filtration which is less effective compared with the current Australian practice of pre-storage leucodepletion. The study concluded that the two methods were equivalent in mitigating the risk of transfusion-transmitted CMV infection. However the secondary analysis of all infections occurring within the first 100 days of transplant showed that the probability of CMV disease in the leucodepleted arm was greater, although infection rates were similar in both arms. The authors noted that there were possible explanations for this outcome and concluded that leucodepletion was an effective strategy to reduce transfusion-transmitted CMV. A later study in 2003 by Nichols et al found that the use of filtered red cells was the primary predictor of transfusion-transmitted CMV, however the use of ganciclovir prevented all but one case of CMV disease. This study highlighted the importance of early CMV detection and effective treatment. Other studies have not shown any differences in infection or disease in CMV seronegative patients receiving CMV seronegative blood components versus leucodepleted blood.

There are several factors which influence the likelihood of a patient acquiring CMV infection and CMV disease, including the chemotherapy protocol, the patients underlying disease and their ability to tolerate side effects of therapy, the institutional CMV monitoring strategy, as well as the use of prophylaxis vs pre-emptive CMV treatment preferences. The risk of CMV disease is considerably mitigated by CMV DNA screening and pre-emptive therapy with ganciclovir or valganciclovir. More recently a test that measures CMV T-cell responses (CMV QuantiFERON) might better define the group at risk of CMV disease. It is also important to note however that the use of CMV quantitative PCR monitoring for at risk patients is not routinely available in Australian hospitals. For this reason it is not feasible to further prioritise within these groups of patients.

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Consensus Statement 4 - CMV Seronegative Blood Access Priority 3

During periods when supplies of CMV seronegative blood components are constrained, the following patients have the lowest priority for transfusion of these blood components and are classified as "CMV Seronegative Priority 3".

- CMV seronegative recipients of autologous stem cell or bone marrow transplants
- CMV seropositive pregnant women having antenatal transfusion with ongoing pregnancy
- CMV seronegative recipients of allogeneic stem cell, bone marrow or solid organ transplants receiving a seropositive transplant.

Following primary infection with CMV, the individual becomes CMV seropositive and is thus both infected and potentially infective for life. Lifelong infection and reactivation facilitates transmission to intimate contacts. 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). To reduce the risk of foetal/neonatal CMV infection, it is recommended that all pregnant women, including those who are CMV seropositive receive CMV seronegative blood components.

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Conclusion

Neither the provision of CMV seronegative blood components nor the provision of leucodepleted blood components completely eliminates the risk of CMV transmission. It is acknowledged that the rates of transfusion-transmitted CMV are both very low, and the two techniques are probably equivalent. However, data to confirm equivalence is not yet available and would require large clinical trials. The Blood Service is undertaking modeling to derive residual risk estimates to inform clinical decision making. The use of CMV quantitative PCR monitoring for at risk patients is not routinely available in Australian hospitals. The vast majority of Australian clinicians do not consider that leucodepleted blood components are equivalent to CMV seronegative blood components which is a significant barrier to implementing a change in clinical practice. However, a recent survey has demonstrated that more than 50% of clinicians would use a leucodepleted blood component for at risk patient populations if a CMV seronegative blood component was not available.