

CTYOMEGALOVIRUS (CMV) - BACKGROUND

PURPOSE

The flowing information provides guidance on the use of CMV negative blood components provided by the blood bank at the Royal Children's Hospital (RCH) including specific patient populations.

RCH blood bank definitions:

- Neonatal patients:
 - Up to 28 days post expected due date *
- Paediatric patients:
 - Infant – 1 to 12 months of age
 - Child – 1 to 12 years of age
 - Adolescent – 13 to 18 years of age

* Note the neonatal extended expiry (ASBT protocol) is valid from birth to 4 months of age

CYTOMEGALOVIRUS (CMV)

Human cytomegalovirus (CMV) is a human herpesvirus with a seroprevalence rate in adults ranging from 40 to 100%. Primary CMV infection can occur following contact with body fluids such as saliva, breast milk or urine, or following transplantation (bone marrow or solid) as well as blood transfusion. Prior to CMV testing and leucodepletion the risk of transfusion-transmitted CMV was reported to be 10 – 60%, but since leucocyte depletion this risk has dramatically declined. Infection in the healthy individual is often asymptomatic or a mild, self-limited viral illness, however in the susceptible individuals such as CMV seronegative infants it can result in severe CMV disease.

Transmission of CMV disease has historically been associated with cellular components (red cells, platelets and granulocytes). Donations manufactured into fresh frozen plasma, cryoprecipitate and plasma-derived components are not screened for CMV, because they are acellular.

Red cells and platelets manufactured by the Blood Services are leucocyte deplete. Leucodepletion refers to the removal of leucocyte (white blood cells) using special filters, from a level of 1×10^8 to $<1 \times 10^6$ leucocytes per unit. Transfusion of leucocyte deplete or CMV seronegative blood components greatly reduces the risk of transfusion-transmitted CMV. However, neither leucocyte depletion nor CMV seronegativity completely eliminates the risk of CMV transmission.

Currently red cell and platelet components (from donors previously testing CMV seronegative and new donors) are screened for the presence of CMV antibodies to provide a CMV seronegative inventory.

WINDOW PERIODS

The most common way to screen for previous CMV infection is serologically looking at the presence of CMV antibodies. After an initial infection with CMV, seroconversion with the development of CMV IgG occurs at about 6 to 8 weeks and antibodies remain lifelong. CMV persists latently in the leucocytes and may be released into the blood stream following reactivation of the latent virus.

A CMV seronegative donor who acquires CMV infection between donations may seroconvert and if tested in the window period may have negative CMV IgG antibody levels and in fact have high viral loads and be at risk of causing a transfusion-transmitted infection. The rate of DNA carriage and viral load is highest in recently seroconverted donors, whereas the risk is much lower in long-term seropositive (> 12 months) donors.

For this reason blood products from CMV seronegative blood donors may not be safer than the provision of blood products from long-term seropositive donors.

THE RISK OF TRANSFUSION-TRANSMITTED CMV INFECTION ASSOCIATED WITH LEUCODEPLETED BLOOD COMPONENTS

The Australian Red Cross Blood Service has calculated a residual-risk estimate for transfusion-transmitted CMV infection from leucocyte-deplete blood components in Australia, by combining results from published literature for the rates of CMV DNA among donors, with WBC filter failure rates. Their model predicts that residual risk for leucocyte deplete, non-CMV antibody tested red cell components is very low, at approximately 1 in 7.8 million. This estimate is well below the threshold of 1 in 1 million (the risk of being struck by lightning) and is considered negligible when contextualizing transfusion risks. For leucocyte deplete platelets the lack of detectable filter failure resulted in a zero risk estimate. The combined risk for red cells and platelets is exceedingly low at 1 in 13,575, 000. (Seed *et al*, *Vox Sang*, 2015)

Table 2—Descriptions of risk in relation to the risk of an individual dying (D) in any one year or developing an adverse response (A)

Term used	Risk range	Example	Risk estimate
High	≥ 1:100	(A) Transmission to susceptible household contacts of measles and chickenpox ⁶	1:1-1:2
		(A) Transmission of HIV from mother to child (Europe) ⁷	1:6
Moderate	1:100-1:1000	(A) Gastrointestinal effects of antibiotics ⁸	1:10-1:20
		(D) Smoking 10 cigarettes a day ⁹	1:200
Low	1:1000-1:10 000	(D) All natural causes, age 40 ⁹	1:850
		(D) All kinds of violence and poisoning ⁹	1:3300
Very low	1:10 000-1:100 000	(D) Influenza ¹⁰	1:5000
		(D) Accident on road ⁹	1:8000
		(D) Leukaemia ⁹	1:12 000
		(D) Playing soccer ⁹	1:25 000
		(D) Accident at home ⁹	1:26 000
		(D) Accident at work ⁹	1:43 000
Minimal	1:100 000-1:1 000 000	(D) Homicide ⁹	1:100 000
		(D) Accident on railway ⁹	1:500 000
Negligible	≤ 1:1 000 000	(A) Vaccination associated polio ¹⁰	1:1 000 000
		(D) Hit by lightning ⁹	1:10 000 000
		(D) Release of radiation by nuclear power station ⁹	1:10 000 000

Calman KC, Cancer: science and society and the communication of risk, *BMJ*, 1996; 3131: 799 – 802

GUIDANCE

The Australian and New Zealand Society of Blood Transfusion, Guidelines for Transfusion and Immunohaematology Laboratory Practice, November 2016 provides guidance on the use of CMV seronegative blood components. Their guidance is that CMV seronegative cellular blood components should be used in pregnant women regardless of CMV status requiring elective transfusions during pregnancy (but not during delivery), intrauterine transfusions, neonates (up to 28 days post expected date of delivery) and granulocyte infusions for CMV seronegative patients. Leucocyte depleted blood components are considered suitable for use (CMV safe) in both adults and children for solid organ transplantation, haematopoietic stem cell transplantation, haematology and oncology patients and immune deficient patients. They advise that institutions consider using polymerase chain reaction (PCR) monitoring for at-risk patients to allow early detection of possible CMV Infection (transfusion-transmitted or otherwise acquired).

In March 2012, the UK advisory committee on the Safety of Blood, Tissues and Organs (SaBTO), published a position statement on the provision of leucodepleted and/or CMV seronegative blood components to reduce the risk of transfusion-transmitted CMV. SaBTO also recommends a restricted list of clinical indications for CMV seronegative blood components. It recommends CMV seronegative blood components for pregnant women, intrauterine transfusions, preterm infants and neonatal transfusion up to 28 days post estimated date of delivery, in addition to granulocyte transfusions. CMV seronegative components are not recommended for immune deficient patients, patients undergoing autologous or allogeneic HSCT or solid organ transplant recipients.

The Canadian National Advisory Committee on Blood and Blood Products (NAC) recently evaluated the literature on the reduction of transfusion-transmitted CMV post leucocyte reduction. In their statement, they recommend that CMV safe (leucodeplete) and CMV IgG seronegative products be considered equivalent **except** for intrauterine transfusion. The NAC recommends that the Canadian Blood Service stop their current process for testing and provision of CMV seronegative units issued to hospital facilities and develop a new process to maintain a small inventory of CMV seronegative blood components for the sole purpose of Intrauterine transfusion. Effective from 23rd October 2017 the Canadian Blood Services will stop testing donor blood for anti-CMV antibodies except for a small inventory of blood components tested for the sole purpose of intrauterine transfusions.

An international forum on the prevention of transfusion-transmitted CMV infection reviewed the policies and risk reduction strategies globally. In Finland there is a national policy that CMV seronegative blood products are no longer available. Since 1994, CMV-seronegative blood products were replaced by leucodepleted blood products with no reports of suspected transmission of CMV by leucodeplete blood products. Similarly in Singapore blood donors are currently not tested for CMV, due to previous studies in blood donors demonstrating a prevalence of 95% positivity for the CMV antibody. No instances of transfusion-transmitted CMV have been reported since 2005. (Liebermann *et al*, *Vox Sang*, 2014)

BACKGROUND

To align with local and international guidelines, a review of the requirements for CMV seronegative blood components has been conducted. CMV seronegative components and leucodepleted components should be considered equivalent in their risk of transmission of CMV.

CMV SERONEGATIVE BLOOD ISSUED AT RCH AND RWH

The RCH and RWH blood banks will provide CMV seronegative blood products to those patients that meet appropriate indications. In an emergency situation where it is not possible to provide CMV seronegative blood products, leucodepleted products of unknown serostatus may be used and will be approved by the duty haematologist. In certain instances CMV seronegative blood products may be given to CMV positive patients to avoid blood product wastage.

Patient group	CMV seronegative	Leucocyte deplete, CMV safe
Intrauterine transfusion	Recommended	If, in an emergency situation, it is not possible to provide CMV seronegative blood products, leucodepleted products of unknown serostatus may be considered.
Pre-term and term infants - Up to 28 days post estimated due date	Recommended	If, in an emergency situation, it is not possible to provide CMV seronegative blood products, leucodepleted products of unknown serostatus may be used.
Neonatal exchange transfusion	Recommended	In an emergency, the use of leucocyte deplete CMV unscreened blood products may be used.
Severe combined immunodeficiency (SCID) patients who are CMV negative (including those undergoing haematopoietic stem cell transplantation (HSCT) #	Recommended	In an emergency, the use of leucocyte deplete CMV unscreened blood products may be used.
Other immunodeficiency patients #	Not indicated	Recommended
Haematology and oncology patients #	Not indicated	Recommended
Allogeneic and autologous HSCT patients #	Not indicated	Recommended
Solid organ transplant patients #	Not indicated	Recommended
Granulocyte infusions	Recommended	
Pregnant women regardless of CMV status - Elective transfusions during the antenatal period of pregnancy for an ongoing pregnancy (but not during delivery)	Recommended	If, in an emergency situation, it is not possible to provide CMV seronegative blood products, leucodepleted products of unknown serostatus may be used

* Equivalent to a single circulating blood volume (~80ml/kg)

Institutions should consider using polymerase chain reaction (PCR) monitoring for at-risk patients to allow early detection of possible CMV infection (transfusion-transmitted or otherwise acquired).