



**NAC EDUCATION DOCUMENT:  
TRANSFUSION AND CYTOMEGALOVIRUS IN THE CANADIAN BLOOD SYSTEM**

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Cytomegalovirus (CMV) is a herpes virus demonstrating seroprevalence ranges of 40- 80% in the general population with variability due to age, geographic location and socioeconomic status.<sup>1,2,3</sup> CMV is transmitted by direct contact with bodily secretions (blood, saliva, urine or breast milk) or tissues. In everyone previously exposed to CMV infection, CMV persists indefinitely in a latent state in mononuclear cells and perhaps other tissues but healthy individuals are generally asymptomatic. In immunocompromised individuals, CMV infections can manifest as serious complications including interstitial pneumonia, hepatitis, retinitis and encephalitis.

The pathogenesis of transfusion-transmitted CMV is uncertain. Although there has been a focus on the possible infectivity of seroconverting blood donors, reactivation of CMV in seropositive subjects has been described as part of normal aging. In addition, later CMV reactivation in a transfused recipient after transfusion of only latently infected cells is also a possible mechanism of CMV transmission. Unlike other transfusion transmissible viruses, the testing performed by blood suppliers is reliant on serologic tests that measure evidence of previous exposure to CMV. Current nucleic acid testing methods are designed as diagnostic tests to detect active CMV infection and are not licensed for screening, as they lack the sensitivity to detect the low levels of CMV DNA in seroconverting blood donors. Moreover, the CMV DNA documented in these individuals may represent non-infectious cell free CMV DNA rather than infectious virions.<sup>4,5</sup> Currently, the components provided when clinicians request CMV negative units in Canada are those where the donor does not have detectable IgG or IgM antibodies. Red blood cell and platelet components that have been prestorage leukoreduced are considered CMV safe components.

Historically, there have been cases of transfusion transmitted CMV infections (TT-CMV) demonstrating transmission rates as high as 60% with fresh warm whole blood<sup>7</sup> but with current prestorage leukoreduction techniques the rate of transfusion transmission has dramatically reduced and is estimated to be 1 in 13,575,000.<sup>8</sup> In 2016, Mainou and colleagues performed a systematic review and meta-analysis evaluating component leukoreduction with



or without donor serology testing in risk reduction of transfusion transmitted CMV. Despite some concerns with respect to quality of some studies, in the 11 studies evaluated, there was no signal of increased risk, demonstrated by clinical and/or laboratory evidence of CMV infection, when comparing leukoreduction to CMV untested units (n=5); leukoreduction to CMV seronegative units (n=3) or leukoreduction alone versus leukoreduction plus CMV seronegativity (n=2).<sup>9</sup>

In 2012, the National Advisory Committee was tasked at evaluating the evidence behind TT-CMV and risk benefit of changing the approach to CMV testing to help Canadian hospital transfusion services and Canadian Blood Services address a) the complexity of marked variability in clinical practice of CMV seronegative requests, b) the limited availability of CMV seronegative components (particularly HLA matched platelet products) often delaying clinically required transfusions and c) the difficulties with managing dual inventory. Due to ongoing improvements in the leukoreduction process and practice pattern evidence from jurisdictions, both within Canada and internationally where CMV seronegative blood components are not being used even for patients considered high risk, it was evident to members on the NAC CMV Working group that eliminating the utilization for CMV seronegative components would reduce component wastage rates, improve the ability of the blood supplier to meet demand, and reduce the cost per unit without compromising patient safety.

As of February 2017, the National Advisory Committee endorsed the following recommendations:

**Recommendation #1**

**The National Advisory Committee recommends that CMV safe (leukoreduced) and CMV IgG seronegative products be considered equivalent *except* for Intrauterine transfusion.**

**Recommendation #2**

**The National Advisory Committee recommends that Canadian Blood Services 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.**

**Recommendation #3**

**The National Advisory Committee recommends that Canadian Blood Services explores the feasibility of providing a small boutique inventory of dually tested (seronegative and NAT) CMV negative blood components for the sole purpose of intrauterine transfusion.**

The provision of CMV seronegative components for intrauterine transfusion (IUT) balanced the risk to this specific population with the capacity of the blood supplier to meet the clinical needs. Intrauterine transfusions in Canada are comparatively infrequent, are performed at highly specialized sites, typically are scheduled in advance, and already require special red cell or



platelet component phenotypes and modifications. Therefore, it is within the capacity of Canadian Blood Services to provide CMV seronegative tested units for this high risk population.

The NAC working group members are aware that there is no current method for CMV nucleic acid testing approved as high throughput screening; however, in the future, it may be possible with the limited inventory required for IUT support to add CMV nucleic acid testing if deemed beneficial to reduce the window period risk in fetuses.

There are many routes by which congenital CMV infection can occur including a) primary infection of a seronegative pregnant woman, b) reinfection of a seropositive woman or c) reactivation of CMV in a seropositive woman, with TT-CMV potentially implicated in (a) and (b). Moreover, fetal transfusion is one of the few clinical settings in which extremely prolonged survival of donor leukocytes have been described, increasing the possibility of CMV reactivation after transfusion of latently infected cells. Of fetuses that become congenitally infected, 10% will demonstrate microcephaly, growth restriction, hepatosplenomegaly, cytopenias, chorioretinitis, CNS impairment and sensorineural hearing loss at birth and have exhibited a death rate as high as 29%. In addition, of those asymptomatic at birth an additional 10-15% will develop symptoms, most commonly sensorineural hearing loss.<sup>10</sup> The clinical significance and burden of these infections, difficulty of monitoring fetal infection and lack of effective *in utero* therapy has prompted the recommendations above.

The same recommendation has NOT been made for low birth weight neonatal transfusion. The primary rationale is that CMV is excreted in breast milk and breast milk transmission is of significantly higher risk than transfusion transmission. A prospective study involving 462 mothers of 539 infants with a birth weight less than or equal to 1500g demonstrated a maternal seroprevalence rate of 76.2%. Twenty seven of the 539 infants developed postnatal CMV infection secondary to CMV positive breast milk at 12 weeks, with 5 exhibiting symptomatic disease and 3 progressing to death.<sup>11</sup> In addition, the risk benefit ratio is also altered with the fact that screening for CMV disease could be performed using either urine, saliva or dried blood spot analysis in most facilities that would care for low birth weight neonates. This would allow for treatment of CMV infection in the postnatal period with ganciclovir and other antiviral agents regardless of the method of infection.<sup>10</sup> There are also some that advocate for the protective nature of passive transfer of CMV antibodies in seroconverted donors in prevention of CMV infection in these breast fed infants. In addition, there has been no evidence of increased neonatal CMV disease in two Canadian facilities, the Hospital for Sick Kids and the Stollery Children's Hospital, who have abandoned CMV seronegative component transfusion for low birth weight infants for more than 10 years.



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**ADDITIONAL RESOURCES CONSIDERED WHEN GENERATING RECOMMENDATIONS:**

**Neonatal Transfusion**

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**Hematopoietic Stem Cell Transplants**

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