

## Cytomegalovirus (CMV) and Transfusion Medicine

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Transfusion plays an important role in modern medicine. Over 14 million red blood cell (RBC) units and the equivalent of 10 million platelet units from whole blood were distributed nationwide in 2004. With enhanced donor screening and testing, the risk of the most serious transfusion-transmitted infections such as human immunodeficiency virus (HIV) and hepatitis C (HCV) has become extremely low (each at less than one per million components transfused). However, due to the high prevalence of CMV infection in the donor population, universal provision of CMV seronegative products for transfusion is not feasible. The intent of this publication is to clarify indications and facilitate the ordering of appropriate blood products by clinicians.

**CMV infection.** CMV is a double-stranded, enveloped DNA herpesvirus. In healthy immunocompetent individuals, primary CMV infection usually is asymptomatic, with seroconversion to an antibody positive status being the only indicator of past infection. Upon resolution of primary infection, the virus establishes lifelong latency (non-productive infection) in its host. Latent CMV viruses are mainly associated with white blood cells, which are responsible for the transmission of CMV by transfusion (TT-CMV) of cellular blood components. Reactivation from latency occurs periodically throughout life in seropositive individuals and provides the stimulus for lifelong antibody positivity. Except during the acute phase of primary infection or reactivation from latency, circulating viremia is typically not a feature. CMV is transmitted by close non-sexual contact (saliva, urine, respiratory droplets, blood), sexual contact, breastfeeding, blood transfusion and organ transplantation.

In the majority of cases, CMV infection does not lead to clinical disease. However, primary CMV infection in immunocompromised seronegative individuals, such as low birth weight infants, some oncology patients and hematopoietic stem cell (HSC) transplant recipients, can cause severe illness with substantial morbidity and mortality. The severity of clinical CMV infection correlates with the severity of cellular immunosuppression and with the CMV serological status of the patient and the blood, organ, or stem cell donor.

**Prevalence of CMV.** Primary CMV infection results in seroconversion with an initial IgM response that overlaps with a developing IgG response. A seronegative test result is not a fail-safe indicator that a blood component is free of CMV risk since components may have been tested while the donor was in "window phase" after exposure, before seroconversion. The length of CMV window period remains to be determined. In addition, some individuals do not seroconvert despite proven CMV infection. Serologic assays for CMV also vary in sensitivity and false negatives can occur.

CMV seroprevalence (the rate of antibodies to CMV) is estimated to be between 20% and 80% in the US population. Seroprevalence increases with age. Although seropositivity is an indica-

### Summary: CMV Reduced-Risk Blood Components

CMV infection does not lead to CMV disease in most transfusion recipients.

Blood components of unknown or positive CMV status can be used for general hospital patients, general surgical patients, full term infants, and otherwise immunocompetent cancer patients.

CMV reduced-risk (either seronegative or leukoreduced) components should be used for seronegative patients in the following categories:

- Pregnant woman
- Intrauterine transfusion
- Premature infants weighing less than 1200g
- Severe combined/variant immunodeficiency
- Hematologic malignancy
- CMV-seronegative autologous hematopoietic stem cell (HSC) or allogeneic HSC recipients or candidates
- Organ transplant: CMV negative recipients of CMV negative organ donor

tor of potential infectivity, only a small proportion (<1%) of seropositive individuals appear to be viremic by PCR.<sup>1</sup> One study found that 0.5 % of healthy seropositive blood donors had detectable CMV DNA in their leukocytes. None of over 500 samples from seronegative donors were positive by PCR.<sup>2</sup> Other studies using PCR have documented CMV DNA in both plasma and cellular components several weeks before seroconversion until several months after seroconversion – likely contributing to the low risk of CMV transmission from seronegative blood donors (window period donation).<sup>3</sup> Currently there are no nucleic acid based tests available to blood collection facilities capable of distinguishing infectious seropositive units from noninfectious seropositive units.

**Transfusion-Transmitted (TT) CMV infection.** TT-CMV infection, like community-acquired CMV, has little clinical consequence (*i.e.*, does not lead to disease) in most immunocompetent transfusion recipients. Early studies established that the incidence of TT-CMV infection from untested nonleukocyte-reduced blood products can be as high as 37%.<sup>3</sup> The risk is proportional to the number of units transfused (donor exposure). In the majority of transmissions, the infection is asymptomatic. In those who develop a primary infection following transfusion, only a few percent develop a mononucleosis-like syndrome 3-6 weeks after transfusion. Full recovery is the rule. Among 76 seronegative children with malignancy receiving transfusion, no cases of seroconversion were documented; while the incidence of asymptomatic community acquired CMV was 1.7% per patient-year in the same population.<sup>4</sup>

In general, the clinical consequences of primary infection are more severe than those of re-infection (co-infection with a different strain) or reactivation from latency. Individuals who are at risk of severe primary infection are seronegative, severely immunocompromised individuals. Symptomatic infection and severe sequelae for the fetus also are associated with a primary infection during pregnancy. The risk of symptomatic TT-CMV is high in multi-transfused preterm infants weighing less than 1200g who are born to seronegative mothers. CMV infection can be fatal in seronegative HSC transplant recipients and clinically significant in seronegative solid organ transplant recipients.

**Prevention of TT-CMV infection.** Two strategies are used to prevent TT-CMV infection in recipients at high risk for CMV disease: 1) leukocyte reduction (LR) by pre-storage filtration (not bedside LR filtration) or apheresis to reduce the number of white cells harboring the virus, and 2) use of cellular products from CMV seronegative donors (CMV-seronegative).

The efficacy of these strategies in preventing TT-CMV infection was established in 1980s and early 1990s. In a landmark study of 502 seronegative HSC recipients, the incidences of TT-CMV infection and disease were statistically identical using filtered blood products vs. CMV seronegative blood products ( $p=1.00$ ) days 21-100 after transplant.<sup>5</sup> However, in a secondary analysis from day 0-100, the rate of clinical CMV disease in patients receiving leukoreduced products was 2.4% vs. 0% in the seronegative arm ( $p = 0.03$ ).<sup>5</sup> The authors state “prospectively defined rules for evaluability were based on data that early infections likely result from the presence and possible reactivation of unrecognized virus acquired before randomization” when commenting on the discrepancy in the secondary analysis. A 2001 Canadian consensus report comparing LR and CMV-seronegative in preventing TT-CMV concluded: 1) Both were effective. 2) Neither was perfect. 3) One was not clearly better than the other, and, 4) no benefit of using CMV-seronegative and leukocyte-reduced components together was established.<sup>6</sup>

The equivalence of leukoreduced and CMV seronegative blood products for preventing TT-CMV remains controversial. In the largest study directly comparing the two products in CMV seronegative HSC recipients, patients who received LR blood components had a higher risk of CMV infection (4%) than those who received CMV seronegative components (1.7%,  $p < 0.05$ ). However, preemptive use of gancyclovir in this study upon detection of antigenemia prevented all but one case of CMV disease.<sup>7</sup> A recent meta-analysis revealed that 12 (1.45%) of 829 recipients of CMV seronegative components from 11 studies and 24 (2.73%) of 878 recipients of leukocyte reduced components from 12 studies developed CMV infection. Among the HSC recipients, the risk of CMV infection was 1.63% (11/674) and 3.01% (21/697) for CMV seronegative and leukocyte reduced components, respectively. When compared with CMV untested/nonleukocyte reduced components, CMV-seronegative components were associated with a 93.1% reduction in the risk of CMV infection. LR components were associated with a 92.3% reduction in risk of infection.

Across three studies that compared CMV-seronegative and safe components to each other, CMV-seronegative components were associated with a 58% reduction in residual risk associated with LR alone ( $p<.05$ ).<sup>8</sup> The author concluded that CMV seronegative blood components are more effective than LR components in preventing TT-CMV infection, but did not find any differences in CMV disease when patients were under active surveillance and received preemptive therapy when CMV infection was demonstrated. Thus it is not known whether the statistical difference in infection rates

between CMV seronegative and leukocyte reduced components translates into clinical benefit in HSC transplant recipients. The combined approach using CMV seronegative donors and LR theoretically may provide a small additional benefit for this group of high risk patients but this has not been demonstrated in an appropriate trial.

The above studies show that breakthrough infections occur with both approaches. For seronegative components, window period infections are the most likely source of failure. CMV seronegative window period donations tend to have higher viral titer and plasma viremia than seropositive donations. The limitations of leukocyte reduction include the potential for inadequate leukoreduction (filter or process failure) and the fact that properly leukoreduced units (allowed by the current standards) may contain up to  $5 \times 10^6$  leukocytes, which may transmit the virus. Methods for pathogen inactivation of blood components are under development, and may mitigate the limitations of current approaches to prevent TT-CMV.

**Summary.** Both CMV seronegative and LR blood components are effective and nearly equivalent in preventing TT-CMV in majority of clinical settings. Any clinical advantage of combining seronegative with LR over either alone remains to be demonstrated in an era of monitoring high-risk patients and preemptive therapy.

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