ASSOCIATION BULLETIN
#02-4

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To: AABB Members

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Re: Update on Provision of CMV-Reduced-Risk Cellular Blood Components

The intent of this bulletin is to provide updated guidance on the use of leukocyte-reduced blood components to reduce the risk of cytomegalovirus (CMV) transmission for transfusion support of “high-risk” seronegative recipients (e.g., CMV-seronegative allogeneic bone marrow transplant patients, low birthweight infants). This topic was thoroughly reviewed in Association Bulletins #97-2 and #99-7.\textsuperscript{1,2} Since these publications were issued, several consensus papers assessing the equivalency of CMV-seronegative and leukocyte-reduced blood components in reducing CMV-transmission risk have been published. In addition, blood components that are leukocyte-reduced by standardized prestORAGE filtration technology\textsuperscript{3,4} have become more widely available in the US. This bulletin summarizes the recent publications and recommends actions to be taken when considering support of patients at risk for CMV disease.

Introduction

CMV is a member of the Herpes virus family and is associated with a spectrum of disease ranging from clinically undetectable infection in the healthy host to severe disease associated with significant morbidity and mortality in the immunocompromised host.\textsuperscript{5} In addition to the well-recognized routes of infection, blood component transfusion has been identified as a vehicle of CMV transmission through passive transfusion of latently infected white cells.\textsuperscript{5} Consequently, leukocyte reduction is thought to be a reasonable strategy to reduce the risk of transfusion-transmitted CMV\textsuperscript{2,6} and in several studies has proven to be effective.\textsuperscript{7-10}
Recent Publications on Prevention of Transfusion-Transmitted CMV through the Use of Leukocyte-Reduced Blood Components

I. Allogeneic Bone Marrow Transplant Recipients

Canadian Consensus Conference

Following review of recent literature and discussion with conference attendees, a panel of experts in Canada was unable to conclude that leukocyte-reduced blood components are equivalent to CMV-seronegative blood components with respect to reducing the risk of transfusion-transmitted CMV. This was due, in large part, to consideration of data derived from the sole randomized controlled study of 502 bone marrow transplant patients evaluating the effectiveness of leukocyte reduction in reducing the risk of transfusion-transmitted CMV. In this study, patients were randomly selected to receive either CMV-seronegative or CMV-untested, leukocyte-reduced (via bedside filtration) blood components. Analysis of data showed no significant difference between the two transfusion groups in the actuarial probabilities of CMV infection and disease between days 21 and 100 after transplantation (1.3% and 0% in the seronegative group and 2.4% and 1.2% in the leukocyte-reduced group; p=1.0 and 0.25, respectively). On the basis of this analysis, the authors concluded that leukocyte-reduced blood components are equally effective as seronegative blood components in reducing risk for transfusion-transmitted CMV. However, a secondary analysis evaluating the probability of infection and disease between days 0 and 100 showed the probability of developing CMV disease was greater in the leukocyte-reduced transfusion group (2.4% vs. 0%, p=0.03), leading to significant controversy over the authors’ conclusions.

Consensus of the University HealthSystem Consortium

In contrast to the Canadian consensus, an expert panel convened by the University HealthSystem Consortium to provide evidence-based recommendations on the use of leukocyte-reduced blood components concurred, after thorough consideration of the same set of data, that blood components that have been processed by current leukocyte reduction methods and manufacturing standards are equivalent to CMV-seronegative blood components.

Other Publications

It is unlikely that a final determination of equivalence of CMV-seronegative and leukocyte-reduced blood components for reduction of CMV-transfusion-transmitted disease will be made, due to the large numbers of patients required for a robust randomized controlled trial. Furthermore, CMV surveillance and employment of preemptive therapy upon detection of CMV antigenemia has led to a broader acceptance of the interchangeable use of CMV-seronegative and prestorage leukocyte-reduced blood components in allogeneic bone marrow transplant patients where both the donor and recipient are CMV seronegative (D-/R-). (In this surveillance approach, recipients are
screened weekly for early appearance of CMV by a sensitive technique, such as polymerase chain reaction, and begun on antiviral therapy (e.g., gancyclovir) as soon as evidence of CMV infection is found, before the appearance of any symptoms.) Using this strategy, Navarios and colleagues\textsuperscript{10} showed, in a retrospective analysis, an incidence of CMV disease of 2.7%. This is comparable to the incidence of CMV disease in allogeneic transplant recipients transfused solely with seronegative blood components. More recently, Nichols et al\textsuperscript{16} reported a 1.1% cumulative incidence of CMV disease in 628 CMV D-/R- allogeneic transplant patients managed with surveillance/preemptive therapy and transfused interchangeably with prestorage leukocyte-reduced or CMV-seronegative blood components. These data confirm the previously reported data that leukocyte-reduced blood components provide the same degree of protection as CMV-seronegative blood components against transfusion-transmitted CMV.

II. Fetuses and Neonates (including infants <1250 grams)

Fetuses and neonates, especially low birthweight infants of seronegative mothers, usually receive CMV-reduced-risk cellular components. However, few recent studies have assessed the effects of strategies to reduce CMV-transmission risk in these situations.

Fergusson et al\textsuperscript{17} recently reported a systematic review of the literature aimed at determining the effectiveness of red cell leukocyte reduction on the reduction of CMV infection and disease. The results of two studies deemed evaluable by these authors to answer this question showed a clinical, but statistically insignificant, benefit of leukocyte reduction in reducing transfusion-transmitted CMV infection. Of note, no infants who received leukocyte-reduced blood developed CMV infection.

Conclusions

While conclusive randomized trials proving equivalency of CMV-seronegative and prestorage leukocyte-reduced blood components for prevention of transfusion-transmitted CMV are lacking, recent analyses of “high-risk” patients monitored for CMV antigenemia transfused interchangeably with CMV-seronegative or prestorage CMV-untested, leukocyte-reduced blood components showed, at most, equivalent rates of infection and disease as previously reported in patients restricted to CMV-seronegative blood.\textsuperscript{15} These data support the use of prestorage leukocyte-reduced blood in lieu of CMV-seronegative blood components.

Recommendations

Although new strategies (e.g., surveillance and preemptive therapy approaches) may reduce the morbidity of CMV infection in some groups of patients, avoidance of transfusion-transmitted CMV remains an important goal for “high-risk” recipient populations. It is recommended that hospital transfusion services, in conjunction with
their transfusion committees and medical services responsible for the care of “at-risk” patients, review internal policies on use of prestorage leukocyte-reduced blood components for prevention of transfusion-transmitted CMV. Furthermore, given the better ability to control leukocyte reduction processes available when the technique is applied prior to component storage, facilities are encouraged to ensure that prestorage rather than bedside leukocyte reduction is utilized in providing CMV-reduced-risk components because of the serious implications of CMV disease.
References


