

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Special Requirements for Blood Transfusions

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H&O What are the options for transfusing blood components with a decreased risk of transmitting cytomegalovirus (CMV) infection?

SGS In the mid 1980s, blood transfusion services in the United States began to transfuse CMV-seronegative cellular blood components (red blood cells, platelets, granulocyte concentrates) to selected recipients who were at increased risk for morbidity or mortality from transfusion-transmitted CMV infections.¹ This practice was more or less standard until evidence began to accumulate that leukocyte reduction by filtration was a convenient and effective alternative. In 1995, investigators reported the results of a large prospective randomized controlled trial and concluded that blood components which had been leukocyte-reduced by bedside filtration carried an equivalent risk of transmitting—or preventing—CMV infection as CMV-seronegative components.² These findings persuaded many directors of transfusion services to discontinue testing donated blood for CMV antibodies and initiated the concept of transfusing leukocyte-reduced blood components as “CMV-safe.”³

In contrast, in 2003, a large retrospective study showed an increased incidence of transfusion-associated CMV infection in recipients of leukocyte-reduced blood products.⁴ The relatively low prevalence of CMV-infective blood components in the contemporary blood supply, combined with CMV seroprevalence rates as high as 70–80% in some community-based donor populations, has created a situation that would require a very large-scale prospective randomized controlled study to deter-

mine whether CMV-seronegative and leukocyte-reduced CMV-safe blood components are equivalent for decreasing the risk of transmitting CMV infection.

The subject of CMV-seronegative (antibody-negative) versus CMV-safe (leukocyte-reduced) has committed advocates on both sides. Presently, there is no standard of practice in the United States. Most, but not all, hospital transfusion services that provide leukocyte-reduced blood components consider them to be “CMV safe” and do not add the additional preventive requirement for CMV-seronegative. Transfusion services that do not provide leukocyte-reduced blood components typically supply CMV-seronegative blood components to susceptible recipients. Some transfusion services, including my own, take the maximally conservative position of supplying leukocyte-reduced components and, whenever the inventory is adequate, CMV-seronegative components to our most susceptible recipients.

H&O What type of patient requires blood transfusions to be CMV-seronegative or CMV-safe?

SGS Patients who are at greatest risk for morbidity and mortality from a primary transfusion-transmitted CMV infection are: 1) low birth weight infants of seronegative mothers, 2) seronegative recipients of autologous or seronegative allogeneic bone marrow transplants, and 3) seronegative recipients of seronegative solid organ transplants, excluding the kidney and heart.⁵ A second category includes patients who are probably at similar,

but unproven, risk: 1) seronegative pregnant women, 2) fetus receiving an intrauterine transfusion, 3) seronegative persons with primary or secondary immunosuppression, and 4) seronegative patients who may be candidates for bone marrow or solid organ transplants.⁵ Not all transfusion services will have an adequate supply of CMV-seronegative or CMV-safe red blood cells on the shelf for emergency transfusions to patients of all ABO/Rh blood types. For this reason, I recommend that those transfusion services that do not routinely maintain an inventory of leukocyte-reduced components maintain a supply of bedside leukocyte-reduction filters. In an emergency, these filters can convert CMV-untested red blood cells or platelets to CMV-safe components.

H&O What technologies are used to test blood components for potential CMV infectivity? Have we seen improvements in the incidence of false-negative results?

SGS Clinical trials evaluating transfusion-transmitted CMV infection established CMV-seronegative (CMV-antibody-negative) blood components as the “gold standard” preventative measure. Laboratory assays for detecting CMV antibodies include latex or particle agglutination, indirect hemagglutination, complement fixation, solid-phase fluorescence, enzyme immunoassay, and solid-phase red cell adherence.⁶⁻⁸ Initially, testing for CMV antibody was performed by using kits for latex or particle agglutination intended for clinical diagnosis. False-negative results were common. Today, most blood center tests for CMV antibodies use automated analysis and highly sensitive assays, often primed with recombinant capture antigens.⁹ False-negative results due to inadequate sensitivity are uncommon. Of course, so-called false-negative results will continue to occur if sampling happens during the 6–8 week seronegative window of a donor’s primary CMV infection. These events are very uncommon, and there are no data to support adding a test for CMV viremia, such as polymerase chain reaction, to decrease the risk of this category of false-negative results.

H&O Have any new developments changed your opinion about the risks of transfusion-transmitted CMV infection?

SGS Yes, there have been 2 important changes. First, most clinical studies that determined the quantitative risk of transfusion-associated CMV infections were conducted in the early 1980s.¹⁰⁻¹² Subsequently, screening procedures to defer potential blood donors who had risk behaviors for HIV and other blood-borne infections, as well as excluding blood testing positive for HIV and

anti-HCV, has significantly decreased the risk of collecting blood from persons who are infective for CMV. Second, recent studies have demonstrated that a significant proportion of transfusion-associated CMV infections are due to the reactivation of the recipient’s prior latent CMV infection.^{13,14} Clearly, transfusion-transmitted CMV infection causes morbidity and mortality in susceptible patients. However, current estimates for the calculated risk of transfusion-transmitted CMV infection should be updated to account for these changes.

H&O What are the pros and cons of universal leukocyte reduction?

SGS The pros of transfusing leukocyte-reduced cellular blood components are a decreased incidence of acute non-hemolytic febrile transfusion reactions in patients with a prior history of febrile reactions, decreased alloimmunization to human leukocyte antigens (HLAs), decreased incidence of refractoriness to platelet transfusions, and decreased transfusion-transmitted CMV infections.¹⁵ Some investigators believe that eliminating allogeneic leukocytes decreases transfusion-related immunosuppression reducing the risk of post-operative infections and recurrence of cancer in certain susceptible patients.^{16,17} The cons are increased cost, delays related to manufacturing and release of filtered components, loss of some blood components due to hemolysis, clogged filters, and other adverse effects of manufacturing-related manipulations.

The primary pro of a policy for universal leukocyte-reduced blood components is that patients who benefit from leukocyte-reduced components are less likely to receive an unfiltered blood component by error. The primary con of a policy of universal leukocyte-reduced blood components has been the additional health care expense of more than \$500 million dollars annually at a time when there is no consensus that there is a substantial medical benefit.¹⁸ Many physicians are not persuaded that clinical trial results have consistently demonstrated a measurable reduction of transfusion-related immunosuppression, which is, potentially, the most important of all benefits.

H&O Which patients require gamma-irradiated blood components and why?

SGS The sole beneficial effect of gamma irradiation of cellular blood components is prevention of graft-versus-host disease in susceptible patients—and the only way to prevent graft-versus-host disease in susceptible patients is to transfuse only gamma-irradiated blood components.^{19,20} The key factor determining who should receive gamma-irradiated cellular blood components (red blood cells, platelets, granulocyte concentrates) is the degree of

their immunosuppression.^{21,22} Recognizing that on the one hand, methods for measuring this risk are imprecise, and on the other hand, that the adverse effects of transfusing irradiated blood are minimal, we irradiate whenever there is a question of significant immunosuppression.

Most transfusion services irradiate all components transfused to a fetus (intrauterine), premature newborn, or immunosuppressed infant. In our hospital, we also irradiate all components for persons with primary immune disease and intensive (ablative) chemotherapy for hematologic malignancies, hematopoietic progenitor cell transplants, and small bowel transplants. In children, we irradiate all components if they are treated with ablative chemotherapy and/or irradiation for hematologic malignancies, neuroblastoma, sarcoma, or any investigative protocol including intensive chemotherapy. We irradiate all blood for persons treated with fludarabine or similar purine analogs.²³

Irradiated blood components are indicated for genetically matched persons, which for practical purposes includes all components from directed donors, family donors, and HLA-matched donors.^{24,25}

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