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# Stability of Cytomegalovirus Antibodies in Plasma during Prolonged Storage of Blood Components

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**Cytomegalovirus (CMV) antibody testing is currently limited by manufacturers' guidelines to specimens stored for 7 days or less. We examined the stability of CMV antibodies in plasma from platelets and whole-blood units during storage using a rapid, automated, recombinant protein-based immunoassay which qualitatively detects total antibody to human CMV. Testing of single-donor apheresis platelets was performed on baseline serum and platelet-free plasma and on platelet-free plasma 8 days later. Indeterminate, positive, and negative CMV antibody results were maintained over time for 97% (75 of 77) of the platelet specimens. For whole-blood units, initial testing of donor serum and plasma obtained from erythrocyte segments took place within 7 days of phlebotomy. Indeterminate, positive, and negative CMV antibody results were maintained on subsequent analyses performed on erythrocyte segments at 2, 4, 6, and 8 weeks for 100% of whole-blood specimens. An important potential benefit of CMV antibody testing of stored platelets and blood is the elimination of a costly, dedicated, CMV-negative inventory. The study suggests that CMV antibody testing can be conveniently and reliably performed on blood components over the entire storage period.**

Cytomegalovirus (CMV), a large, enveloped virus with linear double-stranded DNA, is one of at least seven members of the family *Herpesviridae* known to infect humans. CMV infection is common; by age 30 more than 50% of the population will have had CMV infection. The seroprevalence of CMV in blood donors in the Cleveland area ranges between 50 and 60% (10). Infection with CMV can be acquired during transfusion of cellular blood components via latent virus carried by peripheral blood leukocytes (3). Primary infection with CMV in the immunocompetent recipient can range from an asymptomatic persistent infection to a heterophile-negative mononucleosis syndrome and hepatitis (11, 16). In the immunocompromised host, particularly allogeneic marrow transplant and organ transplant recipients and premature infants, primary CMV infection as a result of transfusion with CMV-positive cellular components is associated with increased morbidity and mortality (7, 9, 12, 15, 17, 19, 22). In this setting, clinical sequelae of primary CMV infection include hepatitis, retinitis, pneumonitis, encephalitis, and gastrointestinal inflammation and ulceration.

Although present U.S. Food and Drug Administration and American Association of Blood Bank Standards do not require that erythrocyte (RBC) units and platelets be routinely tested for CMV antibodies, changes in clinical practice that encompass transfusions to more immunocompromised patient populations have increased the demand for CMV-negative blood components. As a result, the complexity of blood bank inventory management has increased, as have the costs of providing these components. University Hospitals of Cleveland is a 947-bed, tertiary-care hospital whose blood bank maintains a separate inventory of CMV-negative blood components through a standing order with a regional blood supplier. In 1992, the hospital spent more than $100,000 on the provision of CMV-negative blood components.

CMV antibody testing is currently limited by manufacturers' guidelines to specimens stored for 7 days or less. Thus, blood components stored for more than 7 days cannot be tested for the presence of CMV antibodies. Here we report on the stability of CMV antibodies during prolonged storage of RBC units and platelets and analyze the cost-effectiveness of an in-house testing program.

(The study described here was presented in part with a poster at the 1993 Spring American Society of Clinical Pathologists/College of American Pathologists Meeting, Chicago, Ill.)

## MATERIALS AND METHODS

**Patient samples. (i) Platelets.** After obtaining informed consent, single-donor apheresis (SDA) platelets were obtained from 77 donors at the University Hospitals of Cleveland Donor Center by using intermittent flow technology (Mobile Collection System; Haemonetics, Braintree, Mass.). SDA platelets were selected for study because requests for SDA platelets most frequently coincide with requests for CMV-negative platelets. Control samples were obtained from donors by filling a 7-ml red-top Vacutainer blood collection tube from the collection bag of the Mobile Collection System. The serum was separated by centrifugation at 1,200 × *g* for 5 min. As an additional control, day 1 platelet-rich plasma was collected from the temporary reservoir bag, and platelet-free plasma was obtained by centrifugation at 1,200 × *g* for 5 min. Initial or day 1 testing was done in accordance with manufacturers' guidelines and was performed on the day of donation for serum and on day 1 for platelet-free plasma. The average SDA platelet unit at University Hospitals consists of 400 ± 50 ml of platelet-rich plasma with 30 to 40 ml of acid citrate dextrose (ACD).

Prior to release for transfusion, samples of platelet-rich plasma were collected aseptically in 7-ml red-top Vacutainer tubes from SDA platelets that had been stored at room temperature. These tubes were stored at room temperature and on day 8 were centrifuged at 1,200 × *g* for 5 min before final testing of platelet-free plasma. The testing period was selected in order to evaluate changes in antibody reactivity beyond the current shelf-life of the platelets.

**(ii) Whole-blood units.** After obtaining informed consent, whole-blood units were collected from 51 autologous donors at the University Hospitals of Cleveland Donor Apheresis Center. Autologous donors are often older than the allogeneic donor population. They were selected as a study population because a higher percentage could be expected to be CMV positive. Whole blood was obtained in a 7-ml red-top Vacutainer blood collection tube by standard venipuncture before autologous donation, and the tube was immediately stored at 4 to 6°C. Each unit consisted of 450 ± 45 ml of whole blood and 63 ml of

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TABLE 1. Fluorescence signals for serum and platelet-free plasma, Spearman's rank correlation coefficient between serum and plasma signals ($r$), and mean percent changes in fluorescence signals of day 1 and day 8 platelet-free plasma versus those for day 1 serum

| Specimen | $r$ for all units ($n$ = 77) | Nonreactive units ($n$ = 23) | | Indeterminate and reactive units ($n$ = 54) | | | $P$ value[b] |
|---|---|---|---|---|---|---|---|
| | | $r$ | Fluorescence signal[a] | $r$ | Fluorescence signal[a] | % Change (SD) | |
| Serum | | | 0.3 ± 0.1 | | 4.4 ± 2.7 | | NA |
| Platelet-free plasma | | | | | | | |
| Day 1 | 0.961[c] | 0.002 | 0.2 ± 0.1 | 0.963[c] | 4.2 ± 2.6 | −4.6 (15.3) | 0.033 |
| Day 8 | 0.964[c] | 0.326 | 0.3 ± 0.1 | 0.948[c] | 4.0 ± 2.6 | −9.3 (14.6) | <0.0001 |

[a] Fluorescence signals are given as mean ± standard deviation assay value/calibrated cutoff.
[b] $P$ value for mean percent change from serum. NA, not applicable.
[c] $P < 0.0001$.

citrate phosphate dextrose adenine-1 (CPDA-1) anticoagulant (Baxter Health Care Corporation, Deerfield, Ill.). Six attached segments were obtained from each unit of whole blood and were stored in a monitored refrigerator at 4 to 6°C for the entire period of the study. In accordance with current manufacturers' guidelines, initial testing for the presence of CMV antibodies was performed within 7 days of sample collection on serum from the red-top tube and plasma from segments. The red-top tubes were centrifuged at 1,200 × $g$ for 5 min, and plasma from the segments was centrifuged at 1,000 × $g$ for 30 s. Plasma from segments that had been centrifuged at 1,000 × $g$ for 30 s was evaluated during the second, fourth, sixth, and eighth weeks of storage. The 8-week period was selected in order to evaluate changes in antibody reactivity beyond the current shelf-life of the whole blood.

**Fluorogenic ELISA for CMV antibodies.** The fluorogenic enzyme-linked immunoassay (ELISA; Opus; PB Diagnostic, Inc., Westwood, Mass.) used in the present study is a qualitative determination of total antibody (immunoglobulin M [IgM], IgG, and IgA) to CMV in serum and plasma. The assay is based on the use of a recombinant protein which contains conserved sequences from the structural phosphoprotein (pp150) of the human CMV strain AD169. One test well contains the recombinant protein conjugated to alkaline phosphatase. Fifteen microliters of the patient sample-conjugate mixture was added to a glass fiber solid phase which was coated with a recombinant protein which captures IgG, IgM, and IgA. Bound immune complexes converted the substrate into a fluorescent product, and the rate of fluorescence generation was compared with those of stored calibrator values for interpretation of the results. Controls and calibrators were provided by the manufacturer. According to the manufacturer's guidelines, two controls, one positive and one negative, were run once every 24 h. Depending on the number of samples run, the setup time was 30 min, and the time for completion of the assay ranged from 30 to 90 min. Testing of duplicate samples is not recommended.

According to the manufacturer's guidelines, samples were classified as negative, positive, or indeterminate on the basis of the results of the fluorescence signals which were generated from the raw assay values divided by a cutoff value derived from calibrator values. Mean ± standard deviation calibrator values were 0.408 ± 0.111 for the nonreactive samples and 5.81 ± 0.678 for the reactive samples. Negative or nonreactive specimens were defined as those with fluorescence signals of less than 0.8; samples which were considered positive for antibody to CMV or reactive had signals greater than or equal to 1.0. Indeterminate samples were those with signals greater than or equal to 0.8 and less than 1.0.

**Statistical analysis.** The correlation between values for serum and plasma is presented as Spearman rank correlation coefficients because of the nonnormal distributional properties of the fluorescence signals. To test if there were statistically significant differences between the signal data generated by serum and plasma over time, the mean percent changes from the baseline value generated by serum were evaluated. Signal data from blood units with indeterminate and positive initial values for serum were analyzed separately from signal data generated from blood units with negative initial values for serum since preliminary analyses suggested that the correlation of fluorescence signals over time differed for these two groups. In addition, the means and standard deviations of the signal data of blood components are presented.

**Calculations for dilutions.** Calculations for the dilution of plasma by whole-blood units (450 ± 45 ml) containing CPDA-1 calculated under three scenarios (average unit, 450 ml; light unit, 405 ml; heavy unit, 495 ml) demonstrated a dilutional effect ranging from 18 to 21%. The calculations consisted of (i) multiplying the total blood volume by the estimated unit hematocrit (60%) to determine the plasma volume of the unit and (ii) dividing the volume of the CPDA-1 anticoagulant (63 ml) in the unit by the sum of the plasma volume and the volume of the CPDA-1 anticoagulant.

## RESULTS

**Platelets.** Initial testing of serum controls on day 1 revealed that 69% (53 of 77) of SDA platelet units were reactive, 30% (23 of 77) were nonreactive, and 1% (1 of 77) was indeterminate. Qualitative discrepancies between serum and plasma occurred in two cases. One donor had an indeterminate serum specimen (fluorescence signal, 0.95), a nonreactive day 1 platelet-free plasma specimen (fluorescence signal, 0.73), and an indeterminate day 8 platelet-free plasma specimen (fluorescence signal, 0.83). A second donor had an initial reactive serum specimen (fluorescence signal, 1.22), but plasma specimens for both day 1 and day 8 were indeterminate (fluorescence signals, 0.99 and 0.98, respectively). Overall, quantitative analyses for SDA platelet units also demonstrated a strong correlation over time between the mean fluorescence signal values for serum and platelet-free plasma (Table 1). Analyzed separately, the fluorescence signals of CMV-positive units demonstrated strong, statistically significant correlations with the fluorescence signals of their corresponding platelet-free plasma. Not surprisingly, correlations between the fluorescence signals of CMV-negative units and the fluorescence signals of their platelet-free plasma were not statistically significant, suggesting that the signals were mostly random in nature over time for this group. In addition, mean percentage changes from serum levels were statistically significant for CMV-positive units but not for CMV-negative units. The fluorescence signals of negative sera ranged from 0.02 to 0.57, as did the signals of their corresponding platelet-free plasma. The mean changes from the fluorescence signals observed in the CMV-positive units (Table 1) were a 4.6% decrease for day 1 platelet-free plasma and a 9.3% decrease for day 8 platelet-free plasma. These observed decreases were statistically significant for both day 1 and day 8 ($P = 0.033$ and $P < 0.0001$, respectively).

**Whole-blood units.** Initial testing of serum and plasma showed that 72% (41 of 57) of specimens and 71% (36 of 51) of autologous donors were positive for CMV antibodies. In each case in which serum was positive, the corresponding plasma was also positive; a negative result for serum corresponded to a negative result for plasma. No samples had indeterminate reactivities. Subsequent analyses performed on plasma obtained from segments at 1, 2, 4, 6, and 8 weeks demonstrated that qualitative detection of antibodies to CMV was maintained for 100% of the specimens during the entire period of storage at 4 to 6°C. Overall quantitative analyses for whole-blood units also demonstrated a strong correlation over time between the mean fluorescence signal values for serum and plasma (Table 2). As with SDA platelet units, when analyzed separately, the fluorescence signals of CMV-positive units demonstrated strong, statistically significant correlations with fluorescence signals of their corresponding plasma, while the fluorescence signals of CMV-negative units did not. In addition, mean percentage changes from signals for serum

TABLE 2. Fluorescence signals for initial donor serum and RBC segment plasma, Spearman's rank correlation coefficient between serum and plasma signals ($r$), and mean percent changes in fluorescence signals for stored plasma from RBC segments versus those for initial donor serum

| Specimen | $r$ for all units ($n$ = 57) | Nonreactive units ($n$ = 16) | | Indeterminate and reactive units ($n$ = 41) | | | $P$ value |
|---|---|---|---|---|---|---|---|
| | | $r$ | Fluorescence signal[a] | $r$ | Fluorescence signal[a] | % Change (SD) | |
| Serum | | | 0.3 ± 0.2 | | 4.7 ± 4.3 | | NA |
| Plasma | | | | | | | |
| Week 1 | 0.975[c] | 0.397 | 0.3 ± 0.1 | 0.968[c] | 4.6 ± 2.6 | −6.4 (13.9) | 0.005 |
| Week 2 | 0.959[c] | 0.189 | 0.3 ± 0.1 | 0.960[c] | 4.3 ± 4.1 | −8.2 (15.5) | 0.002 |
| Week 4 | 0.971[c] | 0.107 | 0.3 ± 0.1 | 0.975[c] | 4.2 ± 4.0 | −9.5 (12.8) | <0.0001 |
| Week 6 | 0.973[c] | 0.203 | 0.3 ± 0.1 | 0.974[c] | 4.5 ± 4.3 | −5.4 (15.6) | 0.034 |
| Week 8 | 0.969[c] | 0.180 | 0.3 ± 0.1 | 0.964[c] | 4.6 ± 4.4 | −1.2 (16.4) | 0.642 |

[a] Fluorescence signals are given as mean ± standard deviation assay value/cutoff value.
[b] $P$ value for mean percent change from serum. NA, not applicable.
[c] $P < 0.0001$.

were statistically significant for CMV-positive units but not for CMV-negative units. The fluorescence signals of negative sera ranged from 0.05 to 0.68, and signals from their corresponding RBC segment plasma ranged from 0.11 to 0.58. The mean changes from the fluorescence signals observed in the CMV-positive units (Table 2) ranged from a decrease of 1.2% observed at week 8 to a decrease of 9.5% observed at week 4. These decreases achieved statistical significance during all weeks except week 8.

**Cost analysis.** We estimated that 1,500 tests per month would be required to meet the requirement for CMV-negative blood products at University Hospitals of Cleveland. Use of the automated immunoassay system would cost approximately $60,862 annually or $5,072 per month, which would break down to $3.40 per single immunoassay. This estimate is based on instrument reagent rental which would lead to $43,382 of fixed material costs ($37,248 for modules, $5,215 for tips, $559 for sample holder cups, and $360 for calibrators). Labor costs are based on 18 h of work per week and 52 weeks per year, with 3 h required to test RBC units and 15 h required to test platelets each week. The average hourly wage for medical technologists at University Hospitals of Cleveland is $17, with benefits calculated at 24.5% of salary, resulting in $19,810 in annual labor costs. The average hourly wage for technicians is $13, with $15,149 in annual costs. An average of the two salaries results in labor costs of $17,480 per year. Under the current method, the cost of supplying University Hospitals of Cleveland with CMV-negative blood is approximately $9,000 per month or $108,000 per year. Use of an in-house approach would yield a savings of $3,928 each month or $47,138 annually.

## DISCUSSION

An in-house method for CMV antibody screening of blood components can eliminate the need for the blood bank to maintain a dedicated CMV-negative inventory and can allow a just-in-time approach to inventory management in which the number of blood components tested is determined by clinical demand on a daily or a weekly basis. This approach could decrease the waste of CMV-negative blood components and could be cost-effective as well as easy to use, with less technologist intervention, no reagent preparation, no sample pretreatment, and continuous access.

Previous studies have used the latex agglutination method to detect CMV antibody in blood components during storage for up to 7 days for platelet concentrates and 42 days for RBC units (5, 13). In an additional study (6), the latex agglutination method was compared with antibody-specific CMV-IgG and CMV-IgM immunofluorescence assay (FIAX System) of platelets stored for up to 5 days. Although results of the CMV-IgG immunofluorescence assay correlated closely with those of latex agglutination, there were inconsistencies in 14.4% of samples by the CMV-IgM immunofluorescence assay. Our present study, designed to evaluate the stabilities of CMV antibodies after prolonged storage in plasma obtained from platelets and whole-blood units, represents the first, to our knowledge, to use a rapid, automated recombinant immunoassay which qualitatively detects total antibody to human CMV. Since current manufacturers' guidelines limit CMV antibody testing to plasma or serum stored for 7 days or less, a significant percentage of the blood bank inventory of RBC units is currently excluded from CMV antibody testing, despite a shelf-life of 35 to 42 days. In whole-blood units, antibody reactivity status (negative, positive, indeterminate) was maintained for 100% of the specimens, so that prolonged storage did not appear to affect reactivity. However, there was a reduction in the signal intensity from serum to plasma, the largest mean loss of which was 9.5%. This was most likely due to the 18 to 21% dilution of serum by anticoagulation which occurs during processing of whole-blood units. While autologous whole-blood units were used in the present study, since samples were obtained exclusively from the unit segments and not the storage container proper, the results obtained in the present study should be applicable to allogeneic packed RBCs prepared from whole blood collected in a storage container containing a CPDA-1 anticoagulant. In both instances, the unit segments are prepared during the whole-blood phase and represent whole blood containing CPDA-1.

Our results for SDA platelets indicate that antibody reactivity classification was maintained over time for 97% (75 of 77) of the specimens. When the negative threshold is set at a signal value of less than 0.8, on the basis of the manufacturer's guidelines for the immunoassay, then sera and platelets with either indeterminate or reactive signals will not be transfused. Following these guidelines, neither of the two specimens with discrepant results would have been transfused to a patient who required CMV-negative components. The variability of reactivity over time observed in platelet-free plasma specimens obtained from SDA platelets may be due to prolonged storage at room temperature, which may lead to degradation of antibodies, dilution because of anticoagulation, and finally, the

variability associated with the immunoassay method. Examination of fluorescence signal values for serum and platelet-free plasma for the two discrepant samples shows that signal values decreased from serum to platelet-free plasma, which may be due to the effect of dilution on borderline or indeterminate cases or may occur as a result of catabolism of antibodies because of prolonged storage at room temperature. In platelet-free plasma, there was a reduction in the signal intensity from serum to plasma, the largest mean loss of which was 9.3%.

Although the automated immunoassay described here is designed to be a qualitative test, utilization of the data provided by the fluorescence signals permits semiquantitative analysis of CMV antibody reactivity and allows the following observations to be made. First, the percent change in signal intensity was significant for SDA platelets on both days observed (day 1 and day 8) and for whole-blood units during the first through sixth weeks but was not significant during the eighth week of storage. Second, although this quantitative measure achieved statistical significance, overall qualitative test results were comparable over time for 97% (75 of 77) of platelet units and 100% of whole-blood units. Finally, and most importantly, since the apparent dilutional effect is reproducible and consistent, it could be factored into the assay by lowering the threshold for indeterminate reactivity status by slightly more than 10%. In practical terms, the signal intensity could be lowered from 0.80 to 0.70, which would prevent the transfusion of a unit with an indeterminate reactivity for serum and a negative reactivity for plasma. Thus, the dilutional effect observed for all viral marker tests performed on segment samples compared with that observed on undiluted tube specimens (23) can, according to the results of our study, which show a tight correlation between the results for plasma and serum, be appropriately factored into the testing algorithm. In addition, if this tight correlation can be demonstrated for other infectious disease marker tests, it is possible that a similar test algorithm can be developed, when necessary, so that segment samples can be used for these other marker tests.

An alternative to relying on a serological assay to obtain CMV-negative blood components is use of a leukocyte-reducing filter either prestorage or at the patient's bedside (1, 4). Although current commercially available filters can provide in excess of a 3-log-unit reduction in total leukocytes from blood components (21), they have not yet been widely utilized as a substitution for seronegative CMV components. When filters designed to deliver CMV-negative blood components are more widely utilized as expected in the near future, the primary obstacle to their universal use may be financial if the filter is used solely as a means of procuring CMV-negative platelets. A single leukocyte-reducing filter for platelets currently costs $34.50 and an RBC filter costs $18, whereas a single seroassay for CMV by the automated immunoassay system described here, at the present volume of testing, costs $3.40. Given the current seroprevalence of CMV in the Cleveland area of 50 to 60% (1), two to three tests would be required to locate a CMV antibody-negative blood component. Serological assay of blood components would be more cost-effective than using a leukocyte-reducing filter for an SDA platelet unit or a unit of RBCs but would not necessarily be more cost-effective for pooled platelets, which would range from $17 to $51, depending on the number of units tested. However, if the overall goal is to provide the patient with leukocyte-reduced blood components, then the cost of using a filter is only about $10 more than other methods of leukocyte reduction (20). Leukocyte-reduced blood components may also be useful in the prevention of alloimmunization and the accompanying refractory response to platelet transfusion that develops in patients who are chronically dependent on platelets (2, 18). In this regard, however, it is of note that leukocyte filtration has been shown to have limited efficacy in reducing the incidence of nonhemolytic febrile reactions secondary to platelets (8, 14). In addition, the costs associated with leukocyte reduction by filtration given above do not include the costs associated with the necessary verification of leukocyte reduction to a level of $<5 \times 10^6$ leukocytes per transfused unit by tedious counting methods.

The efficacy and cost savings of adding a just-in-time immunoassay for antibodies to CMV to the battery of tests which are already performed in the blood bank were assessed for our institution. After reagent rental, labor, and benefits are accounted for, the annual savings would be $47,138, which would fund a full-time medical technologist position. Further testing with a larger sample size and additional vendors' assays should be done to assess the specific modifications to the cutoff value for negative results that are needed. The results of our pilot study suggest that a just-in-time approach to CMV antibody testing is efficacious and cost-effective.

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