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Transfusion-Transmitted CMV Infections

Clinical Importance and Means of Prevention?

Stuart P. Adler. The frequent acquisition of an active cytomegalovirus infection following blood transfusion has been recognized for at least 15 years. Prospective studies done in the late 1960s and early 1970s of patients transfused during both cardiac and noncardiac surgery demonstrated an average post-transfusion frequency of CMV acquisition of about 30% [1] (as determined by a fourfold rise in CF antibody titer or by viral isolation). These CMV infections occurred with equal frequency in seropositive patients (those having detectable antibody to CMV before transfusion) and in seronegative patients (no detectable antibody before transfusion). The incidence of these infections, however, did appear related both to the number of blood donors and the volume of blood received by these patients. The best overall estimates are between 3 and 12 CMV acquisitions per 100 untis transfused.

The clinical significance of post-transfusion CMV infections in these patients appeared to be minimal. Over 90% of patients remained asymptomatic. Symptoms, when occurring, were those of infectious mononucleosis, characterized by hepatosplenomegaly, adenopathy, and fever. Recovery was complete. Symptomatic infections have been reported both in patients with a primary CMV infection (seronegative before transfusion) and in patients with either reactivation or reinfection (seropositive before transfusion) [2].

Severe symptomatic and even fatal post-transfusion CMV infections do occur in certain groups of immunocompromised patients. These patients include premature infants, transplant recipients, patients undergoing splenectomy, and limited groups of severly immunocompromised oncology patients. The frequency and severity of these infections varies from group to group and is complicated by multiple factors which often prevent definitive conclusions about the role of blood transfusions in CMV acquisition.

The best studied group at risk for post-transfusion CMV infections is premature infants [3, 4]. These infants, especially those with birth weights less than 1,300 g, usually receive multiple blood transfusions in the first several months of life. Of those low birth weight infants lacking maternal antibody to CMV (seronegative) approximately 25–30% acquire CMV infections. Of these, the mortality is about 25%, among which

several cases of disseminated disease have been described [3, 4]. The risk factors for these infants are low birth weight (usually less than 1,300 g), multiple transfusions from seropositive donors, and lack of maternal antibody. Seropositive infants also acquire CMV but transfusions are probably not a frequent source of CMV acquisition for these infants. In these cases acquisition from maternal sources (cervical secretions and breast milk) occurs frequently and is unaffected by the CMV antibody status of blood donors for these infants. No fatalities among seropositive infants acquiring CMV have been described and the CMV-associated morbidity for these infants is under study.

Transplant recipients frequently acquire or reactivate CMV infections after transplantation and these infections are a significant cause of morbidity and mortality in these patients. The importance of blood and blood products for CMV acquisition in these patients is often difficult to evaluate because of the frequent activation of latent CMV either within donor or recipient tissues during post-transplantation immunosuppressive therapy. A significant correlation between blood transfusion and CMV acquisition after renal transplantation has never been demonstrated. However, in none of the studies were all of the variables controlled or monitored – the CMV serological status of recipients, kidney donors, and blood donors. Seronegative heart and bone marrow recipients receiving transplants from CMV seronegative donors do not acquire CMV after transplantation if they receive blood products only from seronegative donors. This includes white cell donors for bone marrow recipients. If either transplant recipient or donor is seropositive, blood donor selection on the basis of CMV antibody status has little impact on post-transplantation CMV acquisition.

Patients undergoing splenectomy, usually secondary to trauma, may acquire severe and even fatal post-splenectomy CMV infections [5]. These patients receive large numbers of blood transfusions during surgery (an average of 42 units). These symptomatic CMV infections presumably occur in patients lacking previous exposure to CMV (seronegative). Prospective studies are required to better define the incidence of symptomatic post-splenectomy CMV infections.

Congenital CMV infection occurring secondary to maternal transfusion has not been reported, but current data strongly indicate that a primary maternal infection is the cause of symptomatic neonatal disease. Hence, seronegative pregnant women requiring transfusion or intrauterine transfusion prior to the onset of labor should receive blood from CMV seronegative donors (see below).

In the United States approximately 20% of all transfused patients are oncology patients and these patients use approximately 20% of all transfused units. Patients with malignancies of all types may develop disseminated and fatal CMV infections. While the incidence of serious CMV infections in this patient group is apparently low, acquisition by these patients may be very frequent. The role of transfusion in CMV acquisition by these patients has not been well studied, although several studies suggest that CMV acquisition is more common among multiply-transfused oncology patients, particularly children with leukemia. Until the role of transfusion and CMV acquisition by oncology patients is better defined, there is little justification for nonselectively trans-

fusing these patients with CMV seronegative blood products.

Post-transfusion CMV infections can be effectively prevented in seronegative patients by providing appropriate blood products from only seronegative donors. That seropositive donors are the source of these CMV infections has been established by several studies [3, 4], particularly those of neonates and bone marrow recipients. The efficacy of donor selection based upon serological evidence of a prior CMV infection has been established and this is currently the most effective means of prevention. A variety of serological tests including EIA and IHA are more sensitive for this purpose than the traditional complement fixation assay. One problem with this method of prevention is that in many parts of the world nearly 100% of donors are seropositive. Presumably seronegative recipients would also be rare in these areas. In Richmond, 40% of random blood donors have antibody to CMV although antibody prevalence is highly age dependent.

Use of CMV seronegative blood products for seropositive recipients is of uncertain value. Seropositive blood recipients may acquire post-transfusion CMV infection either by reactivation of latent virus following transfusion or by reinfection from donor blood products. The relative frequency of these two types of post-transfusion CMV infections in seropositive recipients has not been studied.

Another possible means of preventing post-transfusion CMV infections is the use of leukocyte-depleted blood and blood products. Viable CMV cannot be recovered from the leukocytes of blood donors. Nonetheless, the leukocyte seems a plausible site for CMV latency. CMV can be recovered from the leukocytes of immunocompromised patients or those with a primary CMV infection. Several reports suggests CMV infections can be avoided when frozen deglycerolized red cells are used for transfusion. A problem with these observations is that either the number of patients studied has been small or that the serological status of donors and recipients has not been controlled and/or monitored [6]. However, the use of leukocyte-depleted blood is currently the second best available method likely to be effective in preventing primary infection and perhaps even reactivation and reinfection with CMV following transfusion.

Other possible methods, such as donor screening based upon IgM antibodies against CMV or using filtered blood, have not been studied as means of preventing post-transfusion CMV infections.

In summary, post-transfusion CMV infections should and can be prevented in seronegative low birth weight infants, in seronegative transplant recipients receiving organs from seronegative donors, and in pregnant women requiring transfusion or intrauterine transfusion prior to labor. For other classes of patients, current data is insufficient to justify the extensive use of donor selection or frozen deglycerolized red cells, the only two methods with either proven or likely efficacy.

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J. C. Coleman. The epidemiology of cytomegalovirus infection is very complex. The prevalence of infection as evidenced by possession of antibodies depends on a number of factors, of which age, race and socioeconomic status are but a few. It is therefore very important to remember that any data describing the prevalence of infection must state accurately the nature of the population which has been studied. Furthermore, the unqualified extrapolation of data from one part of the world to another, may lead to confusion.

Post-transfusion cytomegalovirus infection was first described in patients receiving large quantities of blood during open heart surgery. Subsequent studies have shown that in adults the risk of infection is related to the total amount of blood transfused and is not a peculiar complication of extracorporeal perfusion. Neonates appear to be particularly prone to posttransfusion cytomegalovirus infections. In the United States, *Prince* et al. [1] found that 7% of 59 patients who received a single unit of blood and 21% of 72 patients given multiple transfusions had a cytomegalovirus complement-fixing antibody seroconversion. Other estimates of the incidence of cytomegalovirus seroconversion after multiple transfusion have ranged between 23 and 38%.

Among recipients of blood, the clinical response may take many forms, ranging from asymptomatic seroconversion, or a mononucleosis syndrome, or hepatitis to fatal pneumonitis and disseminated infection occasionally seen in neonates and transplant recipients.

Although it would appear obvious that the risk of infection is greater when a cytomegalovirus seronegative recipient receives cytomegalovirus seropositive blood, recent animal models have shown that transfusion of allogeneic leukocytes may induce reactivation of cytomegalovirus infection in a seropositive recipient. Therefore, it may well be that some post-transfusion infections in man are not primary infections, but are due to reactivation of a latent infection.

The development of infection by cytomegalovirus after transfusion appears to depend on a number of factors. Obviously, the number of individual donors is important plus those who receive blood donations from more than two or three donors are at higher risk than those who receive blood from only one or two. The use of fresh blood carries greater risks than that of stored blood, since blood that has been stored longer than 36 h appears to be less likely to transmit infection. Frozen blood does not transmit cytomegalovirus [2]. Leukocyte transfusions

carry an increased risk of transmission [3]. It is generally assumed that the virus is associated with the formed elements of the blood, particularly the white blood cells. However, despite many attempts to isolate cytomegalovirus from the blood of healthy blood donors, only one successful culture has been described in the literature [4]. The presence of cytomegalovirus in the circulation of healthy blood donors therefore lacks confirmation by tissue culture isolation.

In 1970, *Henle* et al. [5] estimated that 5–12% of donors were infectious carriers, this observation being based on immunological response in recipients. However, in the population they studied, the prevalence of cytomegalovirus antibodies was of the order of 50–60%. It therefore follows that not all individuals with antibodies to cytomegalovirus are capable of transmitting the infection. Unfortunately, at this time there is no readily available or reliable test which can detect those amongst donors possessing cytomegalovirus antibodies who are capable of transmitting infection at the time of donation. Were it possible to identify infectious individuals, a much stronger case could be made for the establishment of cytomegalovirus free panels.

Post-transfusion cytomegalovirus infections are probably more significant amongst neonates and those who are immunosuppressed, and although in the United Kingdom the incidence of post-transfusion cytomegalovirus infections is very low, it could be argued that a case could be made for pre-transfusion screening of donors whose blood is intended to be given to the neonates and the immunosuppressed and these individuals should receive only blood from donors known to be seronegative at the time of donation.

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Roger Y. Dodd. Cytomegalovirus (CMV) is a member of the herpes group and, as such, tends to persist after primary infection. Naturally acquired infection is frequent, with serologic evidence of prior exposure approaching 100% in some populations, although clinical manifestations are mild and infrequent. However, CMV commonly causes life-threatening disease in neonates, or in immunocompromised patients. Over the past 20 years, it has become increasingly apparent that CMV infection occurs in a post-transfusion setting, although it is generally not clear whether this represents a primary blood-borne infection or reactivation

of latent CMV in the host. In common with the naturally acquired infection, transfusion-associated CMV appears to be of little consequence in most, if not all immunologically competent patients. In contrast, postoperative CMV infection in tissue and organ recipients is considered to be a frequent cause of mortality or morbidity. In particular, 20–30% of bone marrow transplant recipients die of interstitial pneumonitis, generally ascribed to CMV. Problems have also been noted in renal and cardiac transplant recipients and, interestingly, among patients undergoing splenectomy [1]. Although transfusion is considered to be one source of the postoperative infections, the possibility of transfer of virus in the graft, reactivation of host infection or other iatrogenic or natural routes cannot be ruled out.

The study by *Yeager* et al. [2] on transfused neonates does, however, appear definitive. Transfused infants of CMV seronegative mothers were not infected with CMV unless they received CMV seropositive blood units, implicating the blood itself as the source of infection. Further, the occurrence of death or serious disease was confined to infants of seronegative mothers. These data led *Yeager* et al. [2] to propose that infants of low birthweight should be transfused only with CMV seronegative blood or components. This proposal appears reasonable and has gained some acceptance in the US although a number of groups await the publication of confirmatory studies before implementing policies to reduce transfusion-associated CMV infection among neonates.

The association of infectivity with CMV seropositive blood is a reflection of the persistent nature of CMV infection. In other words, the presence of antibody defines prior infection and thus the potential presence of latent or persistent virus. Hence, CMV seronegative blood is assumed to be free of the virus and its the use of screened products for neonatal transfusions is an appropriate means to reduce the transmission of the virus. Unfortunately, the procedure is logistically troublesome since 50% or more of blood donors have detectable levels of anti-CMV whereas it has been estimated that only 2–3% of donations are actually infectious for the virus. However, at this time there does not appear to be a more specific test to identify those few blood units which are indeed infectious.

A number of diagnostic test procedures for antibodies to CMV are commercially available, and are suitable in greater or lesser degree for routine donor screening. The usual reference method is complement fixation, which cannot be recommended for donor screening purposes on account of the complexity of the procedure; further, it is not available in kit form. Those methods which are commercially available are briefly described below. Each has certain advantages and disadvantages, but an attempt has been made to rank them in order of increasing convenience for blood center use.

The indirect fluorescence assay (IFA) consists of microscope slides bearing fixed, CMV-infected cells. Test samples are applied to the cell substrate, which is subsequently washed; adherent anti-CMV is detected by fluorescence labeled anti-immunoglobulins and the reaction is evaluated microscopically. Enzyme-linked immunoassay (ELISA) tests are based upon the direct sandwich procedure; CMV antigen is linked to the solid phase; enzyme-conjugated antiglobulin preparations are used as a detector. The majority of available tests use

microplate technology, with some minor variations. Somewhat similar is the solid phase fluoresence immunoassay (FIAX), which uses a solid phase antigen in a dip stick format, detecting adherent anti-CMV with a fluorescence-labeled anti-immunoglobulin probe. The procedure is formally equivalent to IFA, but is read macroscopically and quantitatively.

With the exception of ELISA procedures, which can be read by eye, the foregoing methods do require capital equipment. In fact it is also preferable to evaluate ELISA reactions instrumentally. The indirect hemagglutination assay (IHA) does not depend upon instrumentation. It consists of erythrocytes coated with CMV antigen. The presence of anti-CMV agglutinates the cells and the reactions are read on the basis of settling patterns in microtiter plates. Unlike the other procedures, IHA is essentially a one-step assay, which would appear to be an advantage in the blood center. We have found that, with the exception of IFA, these procedures are essentially equivalent in their ability to detect CMV antibodies. IFA gives a seropositive rate of some 73% among random donors from five blood centers in the United States [3] as it does in the Los Angeles area [4], whereas the other tests give a detection rate of about 50% when used on the same sample population. The IHA procedure does identify some additional active specimens relative to ELISA. These are presumed to represent IgM antibodies.

Despite the relative simplicity of tests for anti-CMV, the problems inherent in selecting less than 50% of available blood for delivery to specific patient groups are significant. These difficulties are emphasized particularly where special products or collection methods (i.e. quad packs) are required. Therefore, other approaches to the reduction of transfusion-associated CMV infection have been proposed. Most authors feel that CMV transmission is via the formed elements of blood; the most likely candidate is the polymorph. Thus, it has been suggested that the reduction of leukocyte content in packed red cells may reduce the transmission risk. In many cases, red cells are routinely washed before being transfused to neonates; this procedure is designed to reduce extracellular potassium, but it may have additional benefits in reducing CMV infection. We are currently investigating this possibility. A more stringent approach is to use frozen deglycerolized red cells which appear to have vanishingly low risk of transmitting CMV. Finally, the use of irradiated blood has been proposed but the efficacy of this procedure is unknown.

The situation with respect to other patient groups is much less clear cut. Although it would appear reasonable to reduce the risk of CMV infection for all immunocompromised patients, the following facts must be taken into account: (i) the use of CMV-screened products is inappropriate for seropositive patients; (ii) equally, it is inappropriate for recipients of organs or tissues from seropositive donors; (iii) the majority of immunosuppressed patients receive large numbers of blood products, including platelets and, occasionally, granulocytes; (iv) except among recipients of prophylactic granulocyte transfusions, CMV immune globulin may provide adequate protection from disease [5, 6]; (v) certain patient groups usually present a need foremergency transfusion (i.e. pregnant women, some candidates for splenectomy).

One or more procedures may well prove worthwhile and cost effective for support of

some patients at risk of CMV-associated morbidity or mortality. However, they do not seem to offer any hope for those patients requiring leukocytes. Because such patients generally require large numbers of products, great care must be taken in considering policies in this area.

In summary, the severity of CMV infection in certain patient groups and especially neonates of very low birthweight justifies the adoption of measures to reduce the transmission of infection to these susceptible hosts. Becaue CMV infection is usually benign in immunocompetent patients, screening should be viewed as an issue of compatibility rather than safety. In other words, there should be no prohibition of usage of CMV seropositive blood for the majority of patients. Simple serologic screening procedures are available and they do seem to offer protection. However, the logistic problems of applying such screening are significant, and alternate approaches to the elimination or detection of the virus must be evaluated. Although there is a rationale for supporting transplant patients with CMV-free products, the proportion of susceptible patients may be small and the nature and quantity of the required products is such that it is generally not possible to protect this group of patients.

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F. Carl Grumet. In assessing the clinical importance of CMV infection, critical distinctions must be made for (a) infection vs. significant disease, and (b) immunocompromised vs. immunocompetent (i.e. 'normal') hosts. These distinctions permit clarification of the true hazards, in susceptible hosts, of transfusion-transmitted CMV because interpretation is no longer obscured by a great mass of 'background noise' data from otherwise normal individuals exposed to an otherwise innocuous virus. This clarification is doubly important because most transfusion-transmitted CMV disease is preventable. The pertinent data may be outlined as follows:

(1) Most CMV infection occurs in individuals with normal immune function,

rarely causing anything more than a mild flu-like syndrome. This represents the 'background noise'.

(2) Among immunocompromised hosts (e.g. transplantation recipients, premature infants), CMV infection can cause substantial morbidity and even mortality, particularly during primary infection [1–5]. Disease (rather than infection) risk is substantially modified by the susceptible host's prior immunity. For example, transfused (with blood from seropositive donors) premature infants, with passive CMV antibody from their seropositve mothers, almost never suffer CMV disease despite a 15% infection rate. In contrast, comparably transfused infants lacking passive antibody, because their mothers are seronegative, have a similar infection rate, but have significant CMV morbidity, at a rate of approximately 7.5% overall, or 50% among those infected [1]. These results are consistent with the protection against disease, but not infection, conferred by passive anti-CMV antibody administration in bone marrow transplant recipients [3], again demonstrating that both immunocompetence and prior immunity substantially alter disease risk. In addition to direct cytopathic damage caused by the virus itself, primary CMV infection is associated with lymphocyte hyporesponsiveness, inversions in T cell subset ratios, and increased rates of superinfections with other organisms along with the attendant increased morbidity and mortality [6, 7]. Premature infants affected with only minimal acute or subclinical infection may also be at risk for long term neurological or pulmonary sequelae.

(3) CMV can be transmitted by blood transfusion [1, 3–5] at rates estimated to be from 1 to 12% per unit. When alternate infective sources (e.g. engrafted organs in transplant recipients, breast milk and cervical secretions from infected mothers for premature infants) are adequately eliminated and/or controlled, blood transfusions remain the most important residual source of infection.

(4) CMV transmitted by blood transfusion can cause significant disease in susceptible hosts [1, 3–5]. In the Stanford study [1], of 74 premature infants born to seronegative mothers and transfused with blood from seropositive donors, 10 became infected with CMV, and 5 of these suffered significant morbidity (including 4 CMV-related deaths).

(5) Transfusion-associated CMV infection and disease are unequivocably preventable by use of only seronegative donor blood for transfusion of high risk patients [1, 5]; and provision of such blood is technologically and logistically feasible. Although screening donors for CMV antibody may also detect some noninfective donors, all infective donors are effectively identified. In the Standford study [1] and in subsequent follow-up [*Yeager* et al., in preparation], among 165 premature infants born to seronegative mothers, and transfused with blood from seronegative donors, none developed CMV infection. Several donor screening kits with methodologies acceptable to blood banks (e.g. Elisa, HA, quantitative IF) are commercially available and affordable. Despite the variation among populations in the percentages of seronegative donors (e.g. 50% at Stanford, 25% in a Southern California community blood bank), because the susceptible host populations are small it is feasible to provide sufficient seronegative products for at least the highest risk, immunocompromised patients, premature infants and organ transplant recipients. Because so

few seronegative units are needed, and because CMV does not pose a significant hazard to immunocompetent transfusion recipients, implementation of our screening program to provide seronegative units for immunocompromised hosts has not had any detectable adverse affect upon the 'normal' transfused population [*Preiksaitis* et al., in preparation]. Alternative approaches, such as the use of leukocyte-depleted or frozen-thawed washed red blood cells, to reduce transfusion-associated CMV infection have also been reported; however, I believe screening for seronegative donors is more convenient and less expensive, and has the additional advantage of providing platelet and granulocyte concentrates that should be safe from CMV transmission hazard.

In conclusion, transmission of CMV infection by transfusion is a cause of significant morbidity in high risk (immunocompromised) patients. Transfusion-related CMV disease can effectively be prevented by screening for seronegative donors, and alternative techniques (e.g. frozen blood, leukocyte-poor blood) may ultimately prove to be equally as effective. The continued use of unscreened, routine blood products for very high risk patients (e.g. premature infants born to seronegative mothers) is, in my opinion, unjustifiable at the present time.

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B. Kornhuber, V. Gerein. In immunocompromised patients, especially those receiving immunosuppressive therapy for malignancies or organ transplants, infections are the foremost causes of complications and death. A major roll is played by herpes virus infection. Due to passive immunization against herpes zoster and varicella, these have lost their significance as major complications in immunocompromised patients [1]. Today, cytomegalovirus has gained in importance as a major cause of

complication. The manifest infection is caused by reactivation of a latent infection, blood transfusion (especially granulocyte concentrate) or direct contact with virus carriers. The most significant means of infection in the pediatric population is transmission of the virus by blood transfusion. Here, as well as in other regions, more than 50% of blood donors were found to be CMV-seropositive. We have examined blood units given within 1 month on our oncological ward. 65 blood units were tested of which 35 were positive by the ELISA test for IgG ($\geq$1:160). 2 of the 65 samples also had IgM against CMV. Due to the fact that we did not give whole blood transfusions, we also examined the blood derivatives. These consisted mainly of packed red blood cells which were also filtered to remove a large part of the leukocytes. Of these blood samples, 8 became negative and the remaining 27 showed titre reductions of 75% or more.

In order to demonstrate the increasing contamination of pediatric-oncological patients, data taken from children with ALL and NHL from 1978 to 1982 is reviewed here.

In 1978, 40% of the patients with intensive chemotherapy had CMV antibodies. Of these, only every fourth patient showed clinical signs of infection. In 1982, 66% of the patients had CMV antibodies and 40% of these children showed a more or less clinically relevant CMV infection which on occasion led to interruption of chemotherapy. This development was continuous. The most significant clinical manifestation of the infection was CMV hepatitis which necessitated long pauses in chemotherapy. No deaths were registered due to CMV infection. However, relapse of the primary disease was possibly caused by the interruption of chemotherapy.

Of all employed therapeutic means, the interruption of chemotherapy was the most significant. The application of antiviral drugs (Ara-A, Acyclovir) was not conclusive and the intravenous use of unselected 7-S immunoglobulin preparations showed no statistically evident benefit. Prophylaxis and therapy with CMV hyperimmunoglobulin has been recommended in newer publications [2].

During the past 6 months we have performed our own pilot study in which we gave intravenous 7-S CMV hyperimmunoglobulin to all children starting polychemotherapy. 2 of the 21 children who were passively immunized had CMV-IgG antibodies (ELISA) before commencing therapy. During the first 24 weeks of therapy all children received 50 mg hyperimmunoglobulin/kg intravenously every 2 weeks, followed by 100 mg hyperimmunoglobulin/kg every 4 weeks for the subsequent 52 weeks (this time period has not passed yet).

None of the children developed positive CMV-IgM titres and none developed manifest infection corresponding to CMV disease. All children have CMV-IgG antibodies.

It is practically impossible to avoid inapparent cytomegalovirus carriers by isolating immunosuppressed patients. The complete isolation of a large patient population is not realizable and the isolation of children is intolerable for their well-being. The possibilities to avoid manifest CMV disease in immunodeficient patients today are passive immunization of endangered patients with anti-CMV-IgG in short intervals and the avoidence of transfusion of blood containing leukocytes (leukocyte-depleted packed red

blood cells) [3]. With the high contamination of CMV virus in the normal population one should try to employ only CMV-IgM negative blood donors in immunocompromised patients.

Therapy of CMV infections with hyperimmunoglobulin has not been sufficiently studied to this day. However, our own study has encouraged us to continue our therapy programm.

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Harold V. Lamberson. Clinical significance of human cytomegalovirus (CMV) in my study is now presented. CMV is a member of the herpes family of viruses and as such is capable of latently infecting man. Primary CMV infections produce a broad spectrum of clinical symptomatology ranging from subclinical infection to severe disseminated infection. Approximately 1% of infants are congenitally infected and 5–10% of these manifest signs and symptoms including intrauterine growth retardation, hepatosplenomegaly, thrombocytopenia, hepatitis and neurological manifestations. Regardless of the mode of transmission, most healthy children and adults who acquire CMV seroconvert asymptomatically while a small percentage develop a self-limited heterophile negative infectious mononucleosis-like syndrome. CMV infections acquired by immunocompromised patients may cause, in addition to the heterophile-negative mononucleosis syndrome, persistent fever, pneumonia, hepatitis, pericarditis and encephalitis. CMV characteristically produces more clinically significant disease in severely immunocompromised patients including the fetus in utero, patients receiving chemotherapy for cancer and leukemia, allograft recipients, patients with the acquired immune deficiency syndrome, and low birth weight (<1,200 g) premature infants born to seronegative mothers [1, 2].

The morbidity and mortality associated with CMV infections in immunocompromised patients is difficult to accurately assess. CMV disease in these patients is frequently only one factor in a complex clinical course. It is, however, now well established that low birth weight infants (<1,200 g) born to seronegative mothers are at risk for clinically severe CMV infections if the infections are acquired in the neonatal period [3]. Additionally, it is clear that allograft recipients who develop a primary CMV infection in the immediate post-transplant period are at risk for significant morbidity and mortality.

Reactivation and reinfection with CMV are thought to produce less severe disease [1].

Mode of Transmission

While CMV is considered to be an ubiquitous virus, its mode of transmission is not adequately understood. CMV transmission is thought to require close personal contact or direct exposure to blood and body secretions. Venereal transmission is, no doubt, the most common form of transmission. Other significant modes of transmission are transplacental, and via breast milk, transplanted tissues, and blood products. The studies of *Yeager* et al. [3] and *Adler* et al. [4] clearly implicate transfusion of blood from seropositive donors as a major source of CMV infection in susceptible neonates. The role of blood transfusion in acquisition of CMV by adults is less clearly defined because of the complexities involved in distinguishing primary infection from reactivation and reinfection. It is, however, clear that whole blood, packed red blood cells, platelets and granulocyte products from some seropositive donors are potentially infectious.

Control of Transmission of CMV by Blood Products

The risk of infection with CMV related to blood transfusion has been reported to range from 2.7 to 12% per unit transfused [2]. While the risk of morbidity and mortality attributable to transfusion acquired CMV infection is much smaller, it would seem to be appropriate to reduce this risk for patients who are likely to manifest significant morbidity and mortality related to CMV infection. Patients in this category would include fetuses of seronegative females, low birth weight (< 1,200 g) infants born to seronegative mothers, seronegative transplant recipients receiving transplants from seronegative donors and some selected severely immunocompromised seronegative patients.

Knowledge of the biological properties of CMV and reported clinical trials suggest several approaches to decrease the risk of transfusion transmitted CMV [5, 6]. Efforts to decrease transfusion requirements and expose patients to the minimum volume of blood products and minimum number of donors are warranted. Leukocyte-depleted products (particularly washed frozen deglycerolized red cells) can be expected to be effective since CMV is highly cell associated and does not withstand freezing and thawing. The use of CMV seronegative blood products is recognized to significantly reduce the risk of CMV transmission [3]. Unfortunately, while existing serological methods apparently have sufficient sensitivity to detect donors capable of transmitting CMV, these procedures lack specificity since the majority of seropositive donors do not transmit CMV. A laboratory procedure to identify infectious blood products would greatly simplify the logistics of preventing transfusion-transmitted CMV. Since a large percentage of donors are seropositive and the risk of clinically significant CMV disease is small in all but the above noted high risk groups, the use of seronegative products should be limited to those who are at risk for significant morbidity and mortality related to transfusion acquired CMV.

Additional, and as yet experimental, approaches may prove to be of benefit in reducing the risks associated with CMV infection. Included in this category are active immunization, passive immunization and antiviral therapy [6].

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L. Matter. Although cytomegalovirus (CMV) infection after transfusion of blood is well documented by epidemiological studies, it is difficult to prove transmission of CMV from donor to recipient. The problem of detecting infectious donors will be discussed below. In the recipient, CMV infection is frequently asymptomatic, but it may produce several nonspecific clinical syndromes. The detection of CMV excretion or viremia is the basis for an unequivocal diagnosis of CMV infection. The proof of transmission, however, must rely on the demonstration of the relatedness of CMV strains from donor and recipient by restriction enzyme analysis. Serological diagnosis of CMV infection via blood products is acceptable if a CMV seronegative recipient seroconverts within a few weeks after transfusion. The diagnostic significance of rises in pre-existing antibody titres is less clear; it may indicate reactivation of latent CMV infection. The reliability of CMV-specific IgM for the diagnosis of primary CMV infection has not been established in many clinical settings. Therefore, the evidence for CMV transmission by blood transfusion is indirect; it is strongest on the basis of studies showing prevention of post-transfusion CMV infection by selecting CMV seronegative donors [reviewed in ref. 1].

Epidemiology of transfusion-transmitted CMV infection/disease: according to several prospective studies from 1966 to 1971, the cumulative incidence of CMV infection following open heart surgery with extracorporeal circulation is 45% in CMV-seronegative patients as determined by seroconversion. Clinically, its most frequent manifestation is fever, sometimes accompanied by a mononucleosis-like illness. The disease is self-limited, and there have been no CMV-associated deaths in non-immunocompromised patients. Immunosuppressed patients comprise another high-risk group for serious post-transfusional CMV disease. Pneumonitis and multiple organ involvement including CNS, eyes (retinitis), pancreas and intestine (with hemorrhage), are important factors in determining morbidity and mortality in bone marrow and other transplant patients as well as in patients suffering from neoplastic disease treated with irradiation and cytoreductive drugs. 14–53% of transfused seronegative newborns are infected after transfusion with seropositive blood [2,

3]; clinical manifestations usually appear within 4–8 weeks of transfusion. They include severe life-threatening disease with pulmonary, hematologic or systemic involvement. Preterm babies are at special risk for severe CMV disease (50%) with a high fatality rate (20%) [2]. We have recently shown that in the average adult patient without predisposing conditions the rate of CMV infection after transfusion is not significantly different from the spontaneous seroconversion rate in sex- and age-matched controls [4].

It is difficult to pinpoint reliable markers of infectivity in blood donors. Even after transfusion of blood from CMV seronegative (uninfected) donors, post-transfusion CMV infection and disease may occur in CMV seropositive recipients, probably due to reactivation of latent infection. But the severity of the CMV disease is usually less than in seronegative patients. Seronegative recipients have only very rarely seroconverted after seronegative transfusions, and these instances may represent natural infections or reactivated infections in individuals with very low pretransfusion antibody titres. Although CMV antibodies indicate potential infectivity [2, 3], one would wish to select specifically those donors who will actually transmit CMV to the patient. The detection of virus excretors is not feasible for donor selection. Conceivably, CMV can be transmitted by latently infected donor cells especially in the presence of an allogenic reaction to the transfused cells in the host as has been shown in a mouse model [5]. The value of CMV-specific IgM antibodies as a predictor of infectivity remains to be studied. The total volume of blood transfused and the number of donors involved have repeatedly been shown to correlate with the incidence of post-transfusion CMV infection. Thus, any reduction in transfusion needs will have a favorable influence. The importance of the type of blood products involved is less clear. CMV transmission has not been reported with cell free preparations; transmission seems to require leukocytes. It is controversial if fresh blood carries a higher risk than stored red blood cells.

For the prevention of post-transfusion CMV, the only method with proven efficacy for all blood products relies on the selection of CMV seronegative donors. In populations with very high antibody prevalence, this may seem an inefficient way to find a sufficient number of suitable donors, but in these populations CMV seronegative patients are relatively rare. Ideally, every donation should be tested for CMV antibodies, but in our adult population spontaneous seroconversion, especially in male donors, is so rare [4] that the test may be done at longer intervals. A walking donor program may be sufficient for pediatric transfusion needs. We advocate the use of CMV seronegative blood for: (1) All preterm babies and mature newborns irrespective of their antibody status (maternal IgG antibodies, neonatal CMV specific IgM unreliable). (2) CMV seronegative transplant patients before, during and after transplantation. Because granulocyte transfusions carry an extremely high risk of CMV infection and severe disease in bone marrow transplant patients, such donors should always be CMV seronegative if ever possible to prevent primary as well as reinfection. The organ donor should, of course, be CMV seronegative too. (3) CMV-seronegative patients treated for malignancy with immunosuppressive regimens (especially irradiation in Hodgkin's disease), if available in sufficient quantity.

Patients with primary immunodeficiencies needing transfusion or transplantation should be evaluated individually. The use of CMV seronegative blood for open heart surgery is problematic. Transfusion-acquired CMV infections usually run a benign course in this setting. Prevention of postperfusion CMV infection should nevertheless be attempted (primarily by reducing the overall transfusion requirements), because most febrile illnesses after cardiac surgery necessitate investigations and antibiotic medication, and prolonged hospitalisation. Every blood bank and transfusion center should evaluate the feasibility and extent of a donor selection program according to the number of patients at risk for post-transfusion CMV disease with serious consequence.

The use of frozen red blood cells seems to be an alternative method to prevent transmission of CMV by this product. It necessitates equipment and experience which are not available in all transfusion services in this country. It is also not cost effective. Several live CMV vaccines are being evaluated for the prevention of CMV disease. Many problems with efficacy and safety remain to be solved. The presently available vaccines do not prevent CMV infection. The main purpose of such a vaccine is to prevent congenital CMV disease. Passive immunization using intravenous immunoglobulin preparations containing CMV antibodies may be useful in patients who cannot be protected by selecting seronegative blood or organ donors, predominantly in bone marrow transplantation. Intrauterine CMV infection is not prevented by maternal antibodies, but its clinical manifestation may be mitigated [6]. Passively acquired humoral immunity may in a similar way become operative in a transiently immunosuppressed patient within a limited period of viremia. Several controlled studies are being conducted to clarify these questions. Antiviral agents and interferons have not yet proven useful for (short-term) prophylactic or therapeutic use.

In summary, CMV disease after blood transfusion contributes considerably to morbidity and mortality in certain high-risk patients. It can be prevented by the use of CMV seronegative blood provided by a donor screening program tailored to the needs of the individual transfusion center or blood bank.

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S. Gerald Sandler. In healthy immunocompetent children and aduts, post-transfusion cytomegalovirus (CMV) infection is usually manifested by asymptomatic seroconversion or a mild heterophile-negative mononucleosis syndrome. In contrast, CMV infection may be associated with significant morbidity and mortality in immunoincompetent patients, such as premature newborn infants, children with immunodeficiency syndromes, patients with malignant diseases treated by chemotherapy and radiation, and transplant recipients.

Currently available data do not permit a precise assessment of the clinical importance of post-transfusion CMV infections in most patients, because (1) infections due to exogenous CMV cannot be distinguished from those resulting from endogenous CMV, and (2) the origins of exogenous CMV infections are difficult to determine in these complex clinical settings. Hopefully, new techniques for identifying CMV strains by DNA fragment analysis will provide the information needed to distinguish donor, recipient and environmental isolates and, thereby, clarify the epidemiology of clinically important CMV infections.

Premature low birth weight infants of seronegative mothers have been identified as a subpopulation of immunocompromised recipients in whom post-transfusion CMV infection is associated with significant morbidity and mortality [1]. In this category of immunocompromised transfusion recipients, attempts to prevent primary CMV disease seem appropriate, and transfusion of blood and components from seronegative donors has been reported to be effictive in reducing morbidity and mortality of post-transfusion CMV infections [2].

Other promising approaches to the prevention of post-transfusion CMV infections are currently under investigation, including passive immunization with hyperimmune globulin and plasma, interferon, acyclovir and active immunization with an attenuated live vaccine [3]. For the immediate present, however, the most practical approach to preventing posttransfusion CMV infections is transfusion of blood and components selected from CMV-seronegative donors. Alternatively, transfusion of frozen-washed or other leukocyte-depleted red blood cells from unselected donors may reduce the frequency and severity of primary infections. Candidates for seronegative or other blood products specially processed to reduce CMV infectivity should be limited to persons known to be seronegative.

Since convincing data for clinically important post-transfusion CMV infections are presently limited to selected premature infants, strategies for preventing such infections may focus on the unique needs for transfusions in this defined category of recipients. Blood transfusion in acutely ill newborns is rarely required to treat bleeding, hemolysis or acute anemia. Almost always, transfusions in such infants replace red blood cells lost for repeated blood samplings for clinical laboratory tests. In one hospital, neonatal infants reportedly lost an average of 3.1 ml/kg body weight per day for diagnostic tests while in intensive care [4]. In another hospital, low birth weight infants lost an average of 7–51 ml/kg body weight per 4 weeks – 5–45% of the calculated total blood volume – for diagnostic tests [5]. In a third hospital, 694 of all 781 (87%) red cell transfusions replaced blood lost for diagnostic laboratory tests [6]. The volumes for replacement transfusions in this hospital ranged from 5 to 40 ml. While significant

progress has been made in reducing the volume of blood needed for laboratory tests in pediatric patients, further miniaturization of laboratory equipment and development of alternative monitoring technologies should lead to fewer transfusions and reduce the incidence of post-transfusion CMV infections. Such a preventive approach would not only lower the incidence of post-transfusion CMV infections, but also would reduce the risk of all known and yet-to-be-recognized transfusion-transmitted diseases in this category of recipients.

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F. Streiff, C. Janot, M.E. Briquel. CMV infections may produce a wide spectrum of clinical manifestations depending on the patient's age (congenital infection, perinatally acquired infection, CMV mononucleosis syndrome in children and adults). Of particular interest is the critical importance of disseminated CMW infections in immunocompromised patients, especially those receiving whole-blood or leukocyte transfusions.

Manifestations of CMV infection occur 3 weeks to 2 months after transfusion and can vary greatly from clinically latent seroconversion to mononucleosis with various degrees of fever, hepatosplenomegaly, lymphadenopathy and cutaneous rashes. Interstitial pneumonia, leukopenia or atypical lymphocytosis are less frequently encountered. The high incidence of CMV infection in immunosuppressed patients is now clearly recognized although its mechanism remains partially understood (activation of endogenous virus or introduction of exogenous virus?). In allogeneic bone marrow transplant recipients, CMV is the candidate pathogen most often encountered in interstitial pneumonia. This complication occurs in approximately half of the patients surviving more than 30 days and is fatal in about 60% of cases.

In cases of blood transfusion, the risk of CMV infection is closely dependent on the serologic patterns of the donor and the patient. Seronegative patients receiving blood from seropositive donors are at high risk of infection. At lower risk are seropositive patients transfused with seropositive blood: this is suggestive of a protective effect of the patients' antibodies against the exogenous virus, although the patients may well remain at risk of developing CMV infection from a reactivated endogenous virus.

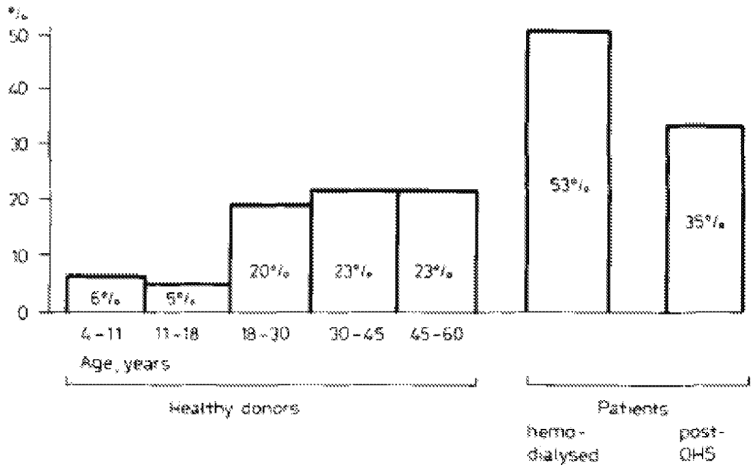

Fig. 1. Repartition of CMV antibodies (IgG ELISA) in blood healthy donors and polytransfused patients.

The role of leukocytes (particularly lymphocytes) seems of major importance since the use of frozen or leukocyte-depleted red cells lowers the incidence of post-transfusion CMV infection [1]. Moreover, it has been shown that the occurrence of CMV infection is higher in patients receiving prophylactic leukocyte transfusions than in control patients receiving no leukocytes or only therapeutic leukocyte transfusions [2].

Diagnosis of CMV infection is based on serologic studies rather than on virus isolation from fluids or tissues. Currently available methods used for defining CMV antibody titers are complement fixation, passive hemagglutination, immunoenzymology, indirect immunofluorescence and radioimmunoassay: complement-fixation is a cheap and simple method, but relatively insensitive compared with immunoenzymology (ELISA) which, in turn, is more expensive and technically difficult. Major problems, however, will remain until there is sufficient standardization of methods and control sera to allow interlaboratory comparisons.

In a recent epidemiologic study we used the complement-fixation, passive hemagglutination and ELISA tests for the determination of CMV antibody in 245 healthy donors (143 males, 102 females) and 149 patients receiving red cell concentrates (101 hemodialysis patients, 48 patients undergoing open heart surgery). Results are reported in figure 1.

Among healthy donors we found striking variations in the prevalence of CMV antibody, depending on ages and socioeconomic conditions. We found no difference between males and females. Transfused patients displayed a different serologic pattern, with a higher prevalence of CMV antibody.

As to prevention in frequently transfused patients (particularly in immunosuppressed patients) several recommendations could be made: (1) use of frozen red cells; (2) careful limitation of the indications for leukocyte transfusion, and (3) selection of seronegative donors, but the technical and financial problems of screening for such donors should be kept in mind.

Several trials of passive immunotherapy in animal and human models have been reported. In seronegative bone marrow recipients, the use of CMV immune plasma has been shown to decrease the incidence of patient CMV infection and interstitial pneu-

monia, especially when leukocyte transfusions are not used [3]. The prophylactic or therapeutic value of CMV immune globulins prepared from selected plasma with high titers of CMV antibody are now under investigation. As a preliminary result from our laboratory, we found CMV antibody titers between 10,000 and 12,000 (ELISA) in different lots of standard immune globulins.

Active immunotherapy with live attenuated vaccines has been experienced with controversial results. It has not reached, at present, large scale utilisation [4].

In conclusion, the tight relations between CMV infection and blood transfusion are now well established. Though they appear more complex than previously expected, they have led to preventive recommendations in patients at high risk of CMV infection based upon selection of seronegative donors, use of leukocyte-depleted blood products and passive immunization.

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Gary E. Tegtmeier. Human cytomegalovirus (CMV) infections are frequently transmitted by blood transfusions for two reasons: first, evidence of exposure to CMV as measured by antibody prevalence is widespread in all donor populations surveyed to date; secondly, in a significant proportion of those antibody positive donors CMV has the ability to establish asymptomatic, latent infections which may then be transmitted to susceptible recipients via donor leukocytes [1]. In fact, this double-stranded DNA virus belonging to the herpes group may be transmitted by blood transfusions more frequently than any other microbe for which reliable tests are available. Only if non-A, non-B (NANB) hepatitis is regularly transmitted without concomitant liver enzyme elevations in the recipient is it likely that another agent could supplant CMV as the most frequent transfusion-transmitted infection. Unfortunately, the lack of sensitive and specific NANB tests prevents this question from being answered at present.

That CMV infections transmitted by transfusions rarely result in overt disease can be seen from numerous prospective studies of pediatric and adult recipients dating back to 1956 [1]. Infection rates ranged from 5 to 67% and averaged 14%, but recognizable disease, largely restricted to patients experiencing primary infections, occurred at a much lower rate of 4%. Higher infection rates were seen in patients receiving larger amounts of blood.

Until recently, CMV's involvement in the etiology of post-transfusion hepatitis (PTH) was uncertain because most earlier prospective studies found similar CMV infection rates both in patients who developed PTH and those who failed to develop PTH. However, an ongoing prospective study of

PTH in cardiac surgery patients in the United States [2] has found that 15% of the cases originally ascribed to NANB were associated with CMV infections. Of 9 cases, all had primary CMV infections, but only 1 had clinically recognizable disease; the remaining 8 had only transient transaminase elevations. Additional studies of prospectively followed PTH cases will be needed to confirm or refute this study's findings.

CMV's significance as a transfusion-related problem arises when immunosuppressed patients acquire the infection. In such patients, infection rates are higher and associated disease is more frequent than in immunocompetent patients. Two groups of patients are at increased risk: premature infants weighing less than 1,200 g and organ transplant recipients. Two recent studies [3, 4] have documented the occurrence of transfusion-acquired CMV infection and disease in premature infants; significantly, infected infants received more than twice the number of donor exposures than uninfected infants. Numerous publications [1] have shown that recipients of kidney, heart, and bone marrow transplants are also at increased risk of CMV infections and disease. The major manifestations of CMV disease include febrile mononucleosis, interstitial pneumonia, anicteric hepatitis, thrombocytopenia, hemolytic anemia, and retinitis. In recipients with intact immunity, the most common clinical manifestation is the mononucleosis syndrome. Although rarely seen in immunocompetent patients, the other features are frequently apparent in immunosuppressed patients.

In renal and cardiac transplant patients the grafted organ appears to be the major source of CMV. Patients developing symptomatic infections are usually CMV seronegative recipients of organs from CMV seropositive donors. Although blood is a potential source of CMV in these patients, it is a low-level risk factor. The situation in bone marrow transplant patients differs in that the CMV antibody status of the marrow donor is not clearly linked to the development of CMV infection in the recipient. The administration of prophylactic granulocyte transfusions enhances the risk of CMV infections in bone marrow recipients, often resulting in serious disease or death [5]. Because bone marrow transplant patients are heavily supported with other blood products, i.e., red cells and platelets, the chances for transfusion-transmitted CMV infections from these sources are significant. To date, however, no published study has controlled for these variables.

How can transfusion-transmitted CMV infections be prevented? I would, first of all, emphasize that preventing CMV infections in most transfusion recipients is unnecessary, because the overwhelming majority of these infections are inapparent and seemingly innocuous. Only in the high risk recipients mentioned earlier should preventive measures be contemplated. One study [3] has shown the efficacy of transfusing blood from CMV antibody-negative donors in averting CMV infections in premature infants. Frozen, deglycerolized red cells have been found to carry a reduced risk of transmitting CMV to renal dialysis patients [1]; additional studies of CMV transmission by frozen-washed or washed red cells are under way in the United States and should provide the data needed to judge the effectiveness of these procedures. At least one investigation is in progress to evaluate the risk of CMV infection from irradiated blood products. Whether stored blood carries a

reduced risk of transmitting CMV remains to be established [1].

The methods reviewed above, i.e., donor screening, freezing and/or washing blood, irradiating blood, and storing blood, are potential control measures which may directly involve regional blood centers, hospital blood banks, or transfusion services. Other approaches to controlling CMV disease in high risk recipients involve administering prophylaxis to the recipient. A recent editorial [6] has detailed these possibilities which include giving antiviral drugs, lymphokines such as interferon or transfer factor, CMV immune globulin or plasma, and CMV vaccinations. All of these potential means of intervention are at varying stages of development. With the possible exceptions of giving CMV immune globulin or plasma to bone marrow recipients and interferon to kidney transplant patients, where recent results have been promising, the safety and efficacy of these approaches remain to be proven.

Although transfusing blood from CMV antibody negative donors appears to prevent CMV infection in premature infants, I believe the widespread application of donor screening for this population should await the completion of several prospective studies of CMV in transfused neonates now in progress in the United States. If the studies confirm the risk of transfusion-acquired CMV disease in this recipient population, then blood products carrying a reduced risk of CMV transmission should be provided. Moreover, such products should be reserved for infants weighing less than 1,200 g at birth whose mothers lack CMV antibodies at the time of delivery.

Regarding organ transplant recipients, it seems prudent to provide CMV seronegative units only to seronegative renal transplant patients receiving kidneys from seronegative donors. If transplant units are not controlling for this major risk factor, i.e., the donor kidney, then providing CMV seronegative donor blood is nonsense. The same caveat applies to cardiac transplant patients. For bone marrow transplant patients straightforward recommendations are more difficult to make. With the marked reduction in the use of prophylactic granulocyte transfusions, the risk of CMV infections should decline. Because these patients are heavily supported with other donor products, I believe that definitive studies must be conducted to assess the risk posed by red cell and platelet transfusions. To routinely provide CMV seronegative donor products for bone marrow transplant patients would be a formidable logistical challenge which should only be undertaken after convincing data from well-designed clinical studies indicate the need to do so.

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T. H. The. Cytomegalovirus (CMV) infections, commonly spread in man, apparently harmless and clinically asymptomatic in the majority of normal individuals are associated with significant morbidity and mortality in patients with a compromised immune system such as premature newborn infants, congenital and acquired immunodeficiency syndromes, malignant diseases treated with intensive chemotherapy and radiation, and immunosuppressed organ transplant recipients. Therefore, transfusion-transmitted CMV infections are becoming increasingly important. However, transmission by transfusions of whole blood, leukocytes or thrombocytes are only one aspect of a more general problem because blood donors with latent CMV infections can excrete or shed infectious virus also into saliva, urine, cervix and semen. In addition, hosts' immunity against CMV antigens is also of importance. In searching for means of preventing life-threatening CMV infections one has to consider also the relationship between CMV and hosts' immune system.

The existence of a virus-specific immunity is reflected by the CMV serological status because individuals with CMV antibodies are more protected against CMV infections than the seronegative ones. Consequently, the clinical symptoms of primary CMV infections are in general more severe than reinfections with other CMV strains or reactivation of latent CMV infections, the so-called secondary CMV infections. Still little is known about the mechanisms involved leading to hosts' immunity against CMV infections. It is important to realize that CMV-infected cells express newly induced virus-specific antigens which are located on the cell membranes (CMV-MA). The immune response to these neoantigens is considered to be important for the recognition and destruction of CMV-infected cells [1]. This is supported by recent studies on the development of humoral and cellular immune responses against CMV-MA shortly after primary CMV infections in man.

Besides this virus-specific immunity, the host's general immune status, background determines also the type of clinical symptoms which appear to be very heterogeneous. They can be placed in 'a spectrum of clinical symptoms' in relation to the hosts' general immune status. Primary CMV infections in adults may cause the 'CMV mononucleosis syndrome' with atypical lymphocytes in the peripheral blood, fever, liver function disturbances, myalgia, arthralgia and exanthema.

Recovery is mostly uneventful. Primary CMV infections in childhood, however, are clinically asymptomatic in most cases. The clinical picture of CMV infection is often entirely different in immunosuppressed organ allograft recipients. The most striking symptoms are spiking and prolonged fever, arthralgia, leuko- and thrombopenia, serum creatinine rise and liver function disturbances, while CMV mononucleosis is not a

distinctive feature, in fact, it is seldom seen. These symptoms are not specific for CMV infections, moreover, they are difficult to differentiate from graft rejection episodes.

The morbidity and mortality of CMV infections in this group is related to the amount of immunosuppressive therapy. Immunodeficiency is related to generalized CMV disease. In CMV-infected transplantation patients a rapid diagnosis of active CMV infection is important because an erroneous raising of immunosuppressive therapy may cause a shift from the early stages of CMV infection to the generalized CMV disease with widespread CMV infection and cytomegalic cells in organs and tissues [2].

The relationship between CMV infections and hosts' immunosuppression appeared to be closely interrelated. Active CMV infections cause a depression of hosts' immune responses. A virus-induced suppression of CMV-specific cellular immunity occurs in CMV mononucleosis syndrome [3] and also in pregnant women and their congenitally infected children. In addition, suppression of general lymphocyte responses are measurable by in vitro lymphocyte stimulation tests to mitogens and antigens. Using monoclonal antibodies against T cell subsets, patients with acute CMV infections show a reversal of the normal ratio of OKT4+ (T 'helper') to the OKT8+ ('suppressor' or 'cytotoxic') T lymphocyte phenotypes. The use of these lymphocyte markers may be of practical importance for the rapid diagnosis of active CMV infections in transplant patients [4]. Clinical observations have confirmed these immunodeficiencies because a high number of other microbial infections were recorded. An increased incidence of infections of an opportunistic nature has been observed following a primary CMV infection in renal, cardiac and bone marrow transplantations.

The above-mentioned observations may have the following important clinical implications.

(1) Cytomegalovirus infections remain an increasing serious medical problem in immunodeficiency patients. It causes different clinical syndromes in relation to host's immune status background. Further, it also causes the likelihood of secondary microbial infections of an opportunistic nature.

(2) Management of these patients requires a rapid and early diagnosis of symptomatic CMV infections in high risk groups (e.g. organ transplantation). For this, sensitive methods for detection of antibody against CMV-early (CMV-EA) and CMV-late (CMV-LA) [5] antigens have been developed. We recently have improved this by a CMV-ELISA method for a rapid screening of sera for IgM antibodies against CMV-EA and CMV-LA. Further, improvement of diagnostic possibilities is provided by a direct detection of CMV antigens and also of CMV genome material in patients' tissues. For the patients with organ transplantation, the diagnosis of acute CMV infection implies a lowering or stopping of the immunosuppressive treatment in order to permit the host to recover from the CMV infection.

(3) Prevention of CMV-infection seems to be required in the above-mentioned special cases with compromised immunity. Serotyping with the CMV-ELISA method for selecting CMV seronegative patient group at higher risk is relevant and practically possible. Furthermore, serotyping of blood donors for donation of whole blood, leukocytes or thrombocytes may be recommended for donations to CMV seronegative recipients in the high risk groups. Prevention of CMV

infection may (partially) be achieved by using leukocyte-free blood instead of whole blood. In addition, the use of stored or frozen blood instead of fresh blood is also recommended.

(4) Application of methods aiming to increase host immunity. Passive immunization has been shown to prevent CMV disease in bone marrow recipients, interferon-alpha has antiviral effect in renal transplant patients and CMV vaccine has been associated with a low incidence of CMV disease after renal transplantation.

Investigation of CMV-induced membrane antigens (CMV-MA) required for an effective host immunity may contribute to a better understanding of the molecular basis of the immune response involved. This may show new roots and may provide the tools for the development of an effective CMV vaccine free of viral DNA.

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C. C. Entwistle, J. O'H. Tobin. CMV was first shown to be the main cause of post-transfusion mononucleosis in the 1960s, since when this virus has been included among the agents known to be transmissible by a transfusion of blood or its products. Most infections are subclinical but up to 10% present with fever accompanied by mononucleosis and/or splenomegaly. This may last for 1–2 weeks or continue for some months, especially in the very young. Premature babies infected by CMV suffer a broader spectrum of illness including pneumonitis, hepatitis, etc. [1]. These superimposed upon the respiratory distress syndrome can lead to considerable morbidity and even death [2].

The infection rate varies with the age of the blood when used and the temperature of its storage: very fresh, unchilled blood being more liable to transmit the virus than stored blood. However, little difference is noted once blood is stored [3]. where rates quoted

in different surveys vary from 2.4 to 12% per unit [4]. In the United Kingdom the rate is about 5%. The rate may be much higher where small infants are given fresh blood straight from a donor [2]. There is no available evidence of the presumably relatively high risk of infection from platelet preparations stored at 22 °C. Blood with any level of CMV antibody is potentially infectious since replicable virus persists in the leukocytes even in the presence of corresponding antibody in the serum although its demonstration has been only rarely accomplished.

One way of avoiding this problem is to identify blood donations with no CMV antibody to be used for those patients at greatest risk. In the UK, few centers have so far followed this approach. In 1975, the Oxford BTS then under Dr. *H. Gunson,* began to provide such blood first for renal transplants and for exchange and other transfusions in neonates. Later blood, and where necessary platelet concentrates, was also supplied for small numbers of children under 16 undergoing open-heart surgery, and for those suffering from leukemia, aplasia and other disorders, especially in younger patients who may be candidates for bone marrow transplantation. Initially, donor screening for CMV antibody was carried out on a small scale, 30–40 samples each week being tested in the Public Health Laboratory by indirect immunofluorescence. In 1978, the Transfusion Service took over and expanded the routine screening to meet the needs of the patients groups specified. Now, about one-fifth of the total donor panel have been tested at some time, including about four-fifths of the group O rhesus-negative donors. A recent study of six different methods for detecting CMV antibody (including immunofluorescence) has suggested that for larger-scale donor screening a micro-hemagglutination test will be the most suitable and practical technique [*Hunt* et al., in press].

The additional cost of identifying and maintaining around 24,000 CMV antibody negative dondors from within the total panel is in the order of £ 1,500 per annum, which is equivalent to 1 patient staying in hospital for about a fortnight. In the USA, the cost has been estimated at about $3 per unit tested [5]. The turnover of selected donors is about the same as that of any blood donor, but in addition some 1–2% are lost each year from acquired new CMV infection. Repeat screening of the panel at each donation is thus necessary.

It is difficult to determine the benefit of supplying blood known to be CMV negative to the patients selected. In renal transplant patients in Oxford, where patients have had to be transfused prior to, or at the time of grafting, new CMV infection has only been acquired from the kidneys of CMV antibody positive donors and not from transfusions (Kurtz and Thompson, in preparation). None of 64 antibody negative recipients given kidneys from similarly negative donors developed CMV antibodies in the ensuing months. Conversely, 38 of 60 such recipients who received a kidney from a positive donor were overtly infected by CMV about 40 days later. The other 22 remained uninfected. The 86 CMV-free patients each received an average of two units of blood. None became infected although the number of cases expected was between 6 and 10.

In exchange transfusions in Manchester and Oxford, the CMV infection rate was about 25% with unscreened blood [2], and about 33% in those given blood known to be CMV antibody positive. Since 1978, about

3,000 units of blood stored less than 5 days have been used for babies receiving exchange and 'top up' transfusions. No case of CMV attributable to transfusion has been diagnosed in spite of close clinical and virological surveillance.

Similarly, no postoperative CMV infection in children undergoing heart surgery has been diagnosed by the virus laboratory [Dr. *J.B. Kurtz*, personal commun.]. Seven bone marrow transplants have been performed in Oxford; the recipients included 5 patients negative for CMV antibody who were given both marrow and multiple blood products all from CMV negative donors. No CMV infection developed in these 5 [Dr. *C. Bunch*, personal commun.].

The justification for providing CMV negative blood to selected patients may be questionable, but certainly in neonatal transfusions it seems unacceptable to expose a sick infant to the risk of unnecessary complications. The role of transfusion in any CMV infection following renal transplantation is uncertain. Although kidneys taken from donors with complement-fixing CMV antibodies are known to be most potent sources of virus, 10% of seronegative recipients given kidneys from suitably negative donors may be expected to develop the infection if given unscreened blood [6]. Where it is patently avoidable, it cannot be considered good practive to risk infecting susceptible patients with CMV through transfusion with all the attendant consequences especially in immunocompromised individuals.

The feasibility of maintaining an adequate panel of CMV negative donors is dependent upon demand for the products concerned, the facilities needed to identify suitable donors, and the prevalence of CMV in the general donor population. Approximately 50% of donors in the Oxford Region are antibody positive, and slightly more than this in the U.K. as a whole; but worldwide the rate is appreciably higher, approaching 100% in some communities. Where the incidence is high [7], there may be insufficient identified seronegative donors available at all times, and other means may have to be sought to reduce the risk of transmitting CMV, e.g. by using frozen and thawed, washed, filtered or otherwise leukocyte-depleted red cells. Such methods are considered a second choice because of the extra effort and expense involved [5]; nonetheless, they may still be cost-effective for blood banks operating in those communities.

Alternatively, in the absence of specific treatment or of an effective vaccine, consideration may be given to conferring passive immunity on selected patients at the time of their greatest risk by judicious use of CMV immunoglobulin. Trials in transplantation so far reported suggest that this form of prophylaxis may substantially reduce symptomatic infection from CMV [8]. However, supplies of the immunoglobulin are severely restricted and the recommended dosage, timing and criteria for its administration are not yet established.

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Editorial Comment

There is almost total agreement among the contributor's on the following two major points: (1) cytomegalovirus infections transmitted by blood and blood products cause serious morbidity and mortality in premature infants and in older immunocompromised patients lacking antibodies to CMV, and (2) prevention of CMV transmission by blood transfusion to high risk recipients is highly desireable and best accomplished at this time by administration of blood that is seronegative for CMV antibodies.

Of further interest are the observations that IgM class antibodies for CMV may add to the specificity of testing donated blood for potential infectivity and that a variety of other methods for preventing CMV transmission to high risk recipients, including leukocyte-poor red blood cells, frozen and washed red blood cells, passive immunization with hyperimmunoglobulin, active immunization, antiviral agents, and minimizing the need for blood transfusion in these patients are under investigation and may add to the clinical and cost-effectiveness of preventing transfusion-transmitted CMV infections in the future.