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Acquisition of Cytomegalovirus Infection: an Update

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INTRODUCTION

Human cytomegalovirus (CMV) is a ubiquitous agent that commonly infects individuals from diverse geographic and economic backgrounds. The majority of persons become infected with this virus at some time during their life; in the United States, as many as 81% of individuals older than 35 years have been exposed to this virus (52). Although most CMV infections are asymptomatic, certain patient groups are at risk to develop serious illness and long-term sequelae from CMV infection. This virus remains the leading cause of congenital viral infection in the United States, a significant cause of transfusion-acquired infections in certain patient populations, and a frequent contributor to morbidity and mortality among organ transplant recipients as well as certain patient groups at risk for human immunodeficiency virus infection.

Ideally, if strategies for the prevention of CMV disease are to be successfully developed, knowledge regarding the epidemiology of the virus is prerequisite. However, a number of features, including a complex natural history, unusual relationship with its human host, ubiquity of infection, and lack of clinical symptoms in most cases, complicate the understanding of the epidemiology of CMV. This review focuses on the currently available information regarding the acquisition of CMV infections since viral acquisition is a key factor determining the frequency or distribution of viral infection in the human population. Following this discussion of viral acquisition, the implications arising from this information are reviewed within the context of developing strategies for the future prevention of CMV infections.

Latency and Reactivation of CMV

The CMVs are an antigenically and structurally diverse group of viruses which are closely related to herpes simplex, varicella-zoster, and Epstein-Barr viruses (159). Following initial infection in the human host, CMV can remain latent, with subsequent reactivation. This characteristic is shared with other members of the herpesvirus family.

Primary infection with CMV is followed by persistence of the virus in a nonreplicating state or at an undetectable level of replication, probably for the lifetime of the host (74). CMV may then emerge from its latent state to produce an asymptomatic or symptomatic endogenous reactivation of infection. Although the factors controlling latency and reactivation are not completely understood, immunosuppression allows for the reactivation of the virus (109).

Molecular Virology

Before discussion of the acquisition of CMV infections, notable features of the viral genome should be mentioned briefly. CMV is the largest herpesvirus, with a linear double-stranded deoxyribonucleic acid (DNA) genome consisting of two covalently bound components designated the long and short unique regions, each flanked by inverted terminal repeats (90, 107). Following infection, the viral genome is slowly transcribed in a regulated sequence, resulting in the serial transcription of three different classes of messenger ribonucleic acids: immediate-early (IE), early (E), and late (L). The IE genes, including the gene encoding for the most abundant IE protein (72 kilodaltons), are transcribed from a restricted region of the long unique sequence of the CMV genome (90). The messenger ribonucleic acid for this major

72-kilodalton IE protein is transcribed more abundantly than any other messenger ribonucleic acid as a result of an upstream regulatory sequence of DNA that competes more efficiently for ribonucleic acid polymerase II (146, 147). These upstream enhancer sequences constitute the first step in the regulation of CMV gene expression. The 72-kilodalton protein is then transported back to the nucleus, presumably to influence the switch from restricted transcription of the long unique sequence to more extensive transcription. A block in the synthesis of IE proteins disrupts any further transcription of the viral genome (138, 145, 147), suggesting that these proteins may play a major role in determining whether a CMV infection is latent, persistent, or productive.

Early genome regions are transiently transcribed after the production of IE proteins, beginning about 4 to 6 h postinfection. However, this transcriptional phase occurs before the onset of CMV replication and in the presence of inhibitors of viral DNA replication, such as cytosine arabinoside (28). CMV viral DNA synthesis then commences in the nucleus 16 to 24 h postinfection (29). Following viral DNA replication, the production of viral L proteins occurs; these proteins primarily represent the structural proteins of the virus particle. Thus, the three phases of transcription suggest that CMV replication proceeds in an orderly and controlled manner and that each phase exerts controls on the progression to the next phase. Regulation of this progressive transcription of the CMV genome has implications for understanding how an otherwise cytopathic virus can consistently induce latent infections in the human host.

ACQUISITION OF CMV BY NATURAL ROUTES

Humans are believed to be the only reservoir for human CMV strains. However, an understanding of the epidemiology of this virus, particularly its transmission, is complicated by the myriad of possible exposure sources. Acquisition of CMV appears to require close or intimate contact with persons who are excreting CMV in their urine, saliva, semen, tears, or other secretions. Studies have shown that infants and children can acquire CMV from other children or from their mothers in utero, at birth, or during the perinatal period (35, 104). Understanding the acquisition of CMV infection following the perinatal period becomes even more complicated due to the continued increase in the number of possible sources of infection.

Intrauterine and Perinatal Periods

Intrauterine. Isolation of CMV from an infant shortly after birth is evidence of an in utero infection; the prevalence of intrauterine infection has been estimated to be 0.2 to 2.5% of all live births (35, 109). Intrauterine CMV infection may have a variable outcome, with only 5 to 10% of infected infants symptomatic at birth. Of note, 5 to 20% of asymptomatic, congenitally infected infants develop late manifestations of CMV infection (neuromuscular disturbances, progressive auditory damage, vision impairment, etc.) in early childhood (24).

Presumably, vertical transmission of the virus to the fetus occurs transplacentally (109). Because of a number of key similarities between the two host systems, a guinea pig infected with guinea pig CMV was used as a model for the study of human congenital CMV infection (54). The data from this study suggested that placental infection can be established early in pregnancy but that significant viral replication may not be possible until later in gestation. More specifically, the data also suggested that the delayed amplification of CMV in the placenta is associated with an increased frequency of fetal infection. However, since CMV has been isolated from the cervix and endometrium during pregnancy, the ascending genital spread of the virus to the fetus from these sites cannot be ruled out completely (80, 109, 128). CMV shedding from the cervix or in the urine is observed almost exclusively in women under the age of 30 (80). The reasons for this observation are unexplained, yet it is of interest that the majority of congenital CMV infections also occur in infants of women under the age of 30 (78).

Current evidence indicates that most symptomatic congenital CMV infections result from the primary infection of the mother (143). However, not all infants of mothers experiencing a CMV seroconversion during pregnancy develop congenital CMV infection (141, 142). Although the risk of cytomegalic inclusion disease in the newborn is usually restricted to those women with primary disease, intrauterine infection with CMV may also occur in infants of women who are seropositive at the beginning of pregnancy. Restriction enzyme analysis of the viruses isolated from these mother-infant pairs has shown the CMV isolates to be identical, suggesting that reactivation of the mother's latent CMV infection served as the source of transmission to the fetus (69, 140).

There are several questions to consider regarding the intrauterine transmission of CMV. First, what factors lead to the development of disease in only some infants whose mothers experience a primary infection during pregnancy? Second, what factors influence the development of symptoms in only a small subset of all infants who become infected with CMV in utero? And third, what factors play a role in the reactivation of latent virus and subsequent intrauterine transmission of virus to the fetus in some pregnant females with substantial levels of serum-neutralizing antibody to CMV? It is evident that these same issues, i.e., identification of specific hosts at risk for disease, particularly those at risk for serious symptoms and sequelae, and an understanding of the factors that influence the crucial host-virus relationship, are pertinent to the development of CMV infections in other patient populations as well. Therefore, these issues will be discussed in a broader sense concerning the transmission of CMV by blood transfusion and organ transplantation.

Perinatal. During the perinatal period, 8 to 60% of infants become infected with CMV usually acquired from maternal sources (109). As mentioned, CMV has been isolated from the cervix and endometrium during pregnancy; longitudinal studies of offspring of those women shedding CMV late in pregnancy have shown high rates of infection (81, 128). Breast milk is the most common route for CMV excretion in lactating women and therefore represents an important source of infection (39, 61, 115, 128). Common practice of breast-feeding and high rates of maternal seropositivity have already been cited as evidence for the major role of breast milk in CMV transmission.

Following the Perinatal Period

Following the perinatal period, there appear to be two additional periods during an individual's life in which the attack rate for CMV infection significantly increases. The first increase in the seroconversion rate occurs within the first 3 years of life, resulting primarily from family contacts. Epidemiological data from antibody prevalence studies have shown that the age-related prevalence of CMV infection

varies among different geographic locations and socioeconomic levels as well (109). In general, CMV is acquired earlier in life in developing countries as compared with developed countries. The reasons for these differences in the age at which CMV is acquired among different populations are unclear, but child-rearing practices appear to influence the incidence of CMV infections in children. Finally, a second smaller, but continual, increase in the seroconversion rate is observed in parallel with the onset of sexual activity.

After the perinatal period, it is more difficult to identify the sources of CMV infections and to elucidate the routes of horizontal transmission. However, during the past few years, significant strides have been made in our understanding through the application of molecular biologic techniques. Genetic diversity among various CMV isolates can be detected by restriction enzyme analysis of purified CMV DNA. Furthermore, the restriction pattern of an endogenous strain in an individual is stable over time (70). The genetic diversity and stability of restriction patterns among CMV isolates have greatly facilitated the investigation of epidemiologic problems, namely, virus acquisition.

Day-care setting. Day-care practices appear to have a profound influence on the incidence of CMV infections. Children attending day-care centers have a higher prevalence of CMV excretion than do children in the general population (3, 109, 110). Compelling evidence for the horizontal transmission of CMV among children in day-care centers has been provided by molecular epidemiologic studies. Using restriction enzyme analysis, Adler (3), Murph et al. (98), and Hutto and Pass (S. C. Hutto and R. F. Pass, Pediatr. Res. **18**:277, 1984) demonstrated that the same CMV strain could be isolated from urine specimens obtained from children attending the same day-care centers. Hutto et al. (72) investigated whether toys and other surfaces could harbor CMV and thereby contribute to the spread of CMV in day-care centers. In agreement with other investigations (45, 139), their results showed that contamination of environmental surfaces with CMV could occur and that isolates could survive on toys for up to 30 min. Restriction enzyme analysis of six CMV isolates recovered during their survey revealed that three of the isolates had identical DNA restriction fragment patterns. Their study clearly suggests that environmental surfaces can serve as potential reservoirs of virus for those individuals in frequent contact with them.

Sexual transmission. To date, several lines of evidence suggest that sexual transmission is responsible for the rise in CMV seroprevalence in young adults. First, the virus is recovered more frequently from cervical secretions and semen than from urine and other sites (84, 128); viral titers in semen were reported to be 100,000 times greater than those in urine. Furthermore, infection with CMV was shown to be more prevalent in women attending a sexually transmitted disease clinic than in women having routine gynecological examinations (75). By determining prevalences of CMV antibody and viral shedding in 63 male sex partners of women with and without CMV infection, Handsfield et al. provided more evidence for the sexual transmission of CMV among heterosexual adults (60). Analysis with DNA restriction enzymes demonstrated that CMV isolates from two of three pairs of infected sex partners were identical and that epidemiologically unrelated strains were distinct. However, conclusions regarding the epidemiology of CMV from this type of analysis must be made with caution, particularly in light of the report by Chandler et al. (20). Her investigation documented the appearance of multiple CMV strains in serially obtained cultures from four of eight women selected from patients attending a sexually transmitted disease clinic. Prior to that report and those of others (36, 70, 91), it had been demonstrated that individuals were usually infected with only a single CMV strain (69, 161).

Concerns

Specific issues surrounding the transmission of CMV by natural routes relate most importantly to preventing CMV transmission to the seronegative pregnant female. For example, there is widespread concern about whether an increased frequency of congenital CMV infections will be seen among infants of seronegative mothers with children in day-care centers. Longitudinal serologic follow-up of seronegative parents of children in day-care centers showed that these parents acquired CMV infection at an increased rate as compared with controls (111). Subsequently, by restriction enzyme analysis, Adler et al. demonstrated not only that children can acquire CMV at a day-care center and excrete the virus in urine and saliva, but also that these children can transmit the virus to day-care workers and to other family members (4, 6). Seven families were studied with a recent case of congenital or maternal CMV infection and a history of maternal contact with a young child excreting virus (112). Restriction enzyme analysis was used to compare viral isolates from family members. Results showed that maternal CMV infection was acquired from a young child and could be transmitted to the fetus. Of the five families that included an infant with a congenital CMV infection, all also included a child of <3 years of age who was excreting CMV and attending a day-care center. This study strengthens the evidence for the transmission of CMV from child to mother and shows that such infections acquired by the mother can, in turn, be transmitted to the fetus.

Similar concerns have been raised for women in childbearing years who work with children in hospitals or other institutions. The risk of spreading CMV infection to these individuals is not fully known and, to date, studies have been conflicting (5, 9, 14, 49, 165). Recently, Demmler et al. investigated nosocomial transmission of CMV in two pediatric units, one with a low prevalence of CMV excretion in patients and the other with a high prevalence (33). Based on this study, the risk of acquiring CMV from hospitalized patients appears to be negligible for hospital nursing staff and occupational, respiratory, and physical therapists. In addition, caretaker-to-patient transmission was not demonstrated in this study, and, in agreement with other studies (5, 139), infant-to-infant transmission in a hospital nursery was infrequent.

As a means of summary, the case report by Demmler et al. (31) describing the transmission of CMV from a husband, a pediatric house officer, to his wife, a registered nurse in a neonatal nursery, is reviewed. In this report, a primary symptomatic CMV infection was documented in the husband. From the time of her husband's illness, the wife, known to be seronegative, was prospectively monitored by serology and cultures. About 3 months after the husband presented with CMV infection, the wife was found to have both immunoglobulin M (IgM) and IgG antibodies to CMV; 1 month later, she began to shed virus identical to that isolated from her husband, but she remained asymptomatic. Five months after her asymptomatic primary infection, the wife became pregnant and subsequently delivered a healthy, full-term infant who was not congenitally infected with CMV. This report illustrates some features of virus trans-

mission by natural routes and also raises some pertinent questions. First, although CMV DNA restriction enzyme analysis demonstrated conclusively that a husband can transmit CMV to his seronegative wife, it remains unclear which form of intimate contact resulted in transmission since the virus was readily isolated from saliva, urine, and semen of the husband, thus illustrating the difficulty in attempting to delineate the routes of natural infection. Second, while it is likely that the semen contained infectious viral particles at the time of conception, it appeared that this source for virus did not play a significant role in the pathogenesis of congenital infection in this particular case. Third, a primary infection in a health care worker does not necessarily mean a hospital-acquired infection. Fourth, host factors appear to play a significant role in determining symptoms during primary infection since the CMV isolates of the subjects were homologous. And last, the transient, intermittent excretion of CMV in individuals experiencing an asymptomatic CMV infection was demonstrated by the investigators. This was underscored by the recovery of virus on only four occasions from 51 attempts to culture CMV. This case report highlights some of the issues surrounding the acquisition of CMV.

ACQUISITION OF CMV BY BLOOD TRANSFUSION AND ORGAN TRANSPLANTATION

Although many individuals are infected, CMV infections, including primary and reactivation infections, are usually mild or asymptomatic in immunocompetent individuals (104). However, infections in certain immunocompromised patients may result in clinically severe CMV disease. Low-birth-weight preterm neonates, allograft recipients, splenectomized patients, and patients receiving immunosuppressive chemotherapy are all at increased risk for serious CMV disease and long-term sequelae (104). Primary, reactivation, and reinfection are the three possible types of active CMV infections that can occur in these patients. In addition to previously described natural routes of infection, introduction of presumably latently infected organs and the almost universal requirement for multiple blood transfusions markedly increase potential exposure to CMV in the immunocompromised patient (16, 66). A mononucleosislike syndrome followed by pneumonia are the two most common manifestations of CMV infection superimposed upon immunosuppression. In general, the major finding in any immunocompromised, symptomatic patient is persistent fever commonly associated with malaise, myalgia, arthralgia, anorexia, fatigue, and night sweats. Interstitial pneumonia due to CMV is the major presentation in bone marrow transplant patients, with a reported incidence of 20 to 45% and an associated mortality rate of 80 to 90% (26, 92, 134).

Risk Factors

Understanding the acquisition of CMV infections in the immunocompromised patient is difficult and, in some instances, controversial due to the complexity and interdependency of many factors that lead to CMV infection. An in-depth examination of all factors is beyond the scope of this review. Therefore, this discussion focuses primarily on the source(s) of CMV infection and the proposed mechanisms for transmission; only key risk factors are highlighted.

Risk factors for acquiring CMV infection are varied and complex. The requirements of the patient for irradiation, cytotoxic drugs, and antilymphocyte and antithymocyte globulin, superimposed upon the underlying disease, lead to expression of varying degrees of virulence and reactivation of latent virus (37, 47, 56, 66, 114). For example, results of a study by Peterson et al. (117) indicated that immunosuppression with cyclosporine plus low-dose prednisone was less likely to predispose renal transplant recipients to the development of CMV-related pneumonia than a regimen of antilymphocyte globulin, azathioprine, and prednisone in higher dosages. Regimens for immunosuppression vary considerably between transplant units and cancer chemotherapy protocols; therefore, rates of CMV infection and the severity of CMV disease differ between centers (66, 117).

Factors that determine the presence and degree of symptoms resulting from CMV infection are incompletely understood, although the source of viral infection, intensity of the immunosuppressive regimen, and degree of host-graft incompatibility all contribute to varying degrees (37, 67). Assessing the contribution of such factors tc the acquisition of CMV infection is complicated further by diverse treatment modalities and underlying diseases of the host. Nonetheless, a major risk factor for developing overt CMV-related disease in an immunocompromised individual is associated with the serologic status of the blood product or organ donor. Recent studies have demonstrated that transfusion-associated CMV (TA-CMV) infections are associated with receipt of blood from CMV-seropositive donors (7, 164). In bone marrow transplant patients, blood products from seropositive donors, particularly leukocyte-containing products, have been implicated in the transmission of CMV since these patients receive massive granulocyte transfusions (64, 113). Some kidney transplant recipients are also at significant risk for CMV infections, although the role of primary infection versus endogenous reactivation in the production of symptomatic illness is still not completely resolved. The donated kidney is presumed to be the major source of CMV transmission to seronegative recipients; when an allograft donor is seropositive and the recipient is seronegative, primary infection develops in 65 to 75% of such recipients (13, 117). In contrast, seropositive recipients are believed to reactivate endogenous CMV or be infected by exogenous virus from the kidney of the seropositive donor (21, 113, 117, 130). For the most part, symptoms are associated with primary CMV infections (15, 37, 148). Other noteworthy risk factors for primary CMV disease are age, because patients with primary infection are generally younger (37), and CMV viremia, because there is a strong association between symptomatic CMV infections and viremia (37, 114). Additional questions have been raised regarding whether the serologic status of the donor might also play a role in the CMV-seropositive recipient developing bacterial or fungal superinfection (13, 17).

The complexity of risk assessment in this patient population is underscored by a recent study by Gorensek et al. (56). In this prospective study of 34 consecutive heart transplant recipients, 23 episodes of CMV infection were identified, with 19 occurring 120 days posttransplant. Fifteen potential risk factors for each of the 19 episodes were evaluated by statistical analysis; many of the traditional risk factors such as age of recipient and number and type of blood products transfused were determined not to be significant in this study.

Blood Transfusion

Generally, CMV infections associated with high morbidity and mortality in immunocompromised patients, excluding

those individuals with the acquired immunodeficiency syndrome (AIDS), are believed to be transmitted iatrogenically by blood transfusion and organ transplantation. A large body of inferential data supports transfusion transmission of CMV from seropositive blood donors to susceptible recipients in a variety of settings (77, 85, 164); the reader is referred to the excellent article by Adler for a more extensive review of this literature (2). Subsequently, Tolpin et al. provided the first biochemical and molecular evidence for TA-CMV infection (153). About 3% of normal blood donors have been found to be viruric and thus actively infected with the virus at the time of donation (77). In one study, 2 of 35 healthy blood donors had CMV isolated from peripheral blood (34); however, several large studies on >1,500 blood donors have failed to confirm these observations (11, 96, 116, 146, 160). The failure to detect CMV in blood products in these various studies might be due to cultural sampling error, if only a small percentage of leukocytes are infected. Nonetheless, despite this convincing evidence in support of TA-CMV disease, the precise mechanisms for transmission of the virus by transfusion remain undefined.

To date, two hypotheses have been investigated as possible mechanisms for CMV transmission by blood. First, since CMV can reside in a latent state in the infected host, it has been proposed that all CMV-seropositive blood donors can transmit latent virus (2, 12, 65); following transfusion, latent virus is reactivated and causes active CMV infection in the recipient. Yeager and colleagues published an excellent study of TA-CMV infections in newborns (164). Infections due to CMV occurred in 13.5% of 74 susceptible infants who received blood from one or more donors with CMV antibody titers of ≧8 as measured by the indirect hemagglutination test for serum antibody. Fatal or serious infections developed in 50% of the infants; however, no infections occurred among 90 susceptible infants who received blood from CMV-seronegative donors only. These results strongly suggest that latent CMV is transferred from donor to recipient during blood transfusion. This hypothesis was further supported by an estimated CMV carrier rate in blood donors of 50% following a prospective study of posttransfusion CMV infections in exchange-transfused neonates (81). Other indirect evidence was provided by Waner et al. (158), who reported multiple fluctuations in CMV antibody titers when normal donors of blood for plasmapheresis were followed longitudinally for over 1.5 years. Of note, titers fluctuated between significant and undetectable in at least 20% of these individuals.

The frequency with which the transfusion of latent virus to a recipient occurs, followed by reactivation and infection, depends on a number of factors. First, the quantity of cells transfused appears to be a key factor (2, 7, 12, 83, 151, 164). Pretransplant blood transfusions are routinely given to renal transplant patients since they appear to increase the survival of the subsequent graft (103, 106). It should be noted, however, that a review of recent transplantation data revealed that the beneficial transfusion effect on kidney graft survival is significantly reduced (105). Nonetheless, Chou and co-workers (22) reported that pretransplant leukocyte transfusions enhanced graft survival with a low risk of CMV transmission, even when recipients were exposed to several donors. In marked contrast to the high risk of CMV infections in bone marrow transplant patients, who receive almost 100-fold more cells by granulocyte transfusions, this finding is consistent with the idea that a substantial number of cells is usually required to transmit CMV infection. Second, the extent to which the leukocytes of a given seropositive donor contain latent virus might also play a role (22). Finally, based on a high rate of CMV transmission among recipients of two transfusions of donor-specific, HLA-haploidentical blood which was seropositive for CMV, Chou et al. suggested that the rate at which the infused cells are destroyed by the immune system of the recipient may play a role in the transmission of latent CMV and its subsequent reactivation in the recipient (22). Furthermore, they suggested that, with the second transfusion, the same immunological mechanism that enhanced graft survival might also enhance the survival of the infused, latently infected cells. Therefore, it is possible that transfused cells act to elicit a graft-versus-host response in the recipient, leading to the activation or enhancement of latent virus from the cells of the donor or recipient. In a more general sense, the suggestion has been made that individuals perfused with large volumes of whole blood experience subsequent changes in their cell-mediated immunity which allow the expression of latent virus (2).

Some evidence also suggests that actively infected, rather than latently infected, donors transmit infections. First, the number of individuals who are viremic or are actively shedding CMV is significantly lower than the antibody prevalence in the donor population, thereby suggesting that only a subset of blood donors can transmit CMV infection. However, as previously discussed, all attempts to confirm this hypothesis have failed, with one exception. Second, those studies showing a significant correlation between the number of transfused units and the likelihood that seronegative patients will acquire CMV also lend support to the hypothesis of a subset of infectious blood donors (2, 7, 67, 163). However, in a prospective study of seroconversion among hospitalized patients who were initially seronegative for CMV and received blood transfusions, oncology patients did not seroconvert, even when they were being treated with cytostatic drugs or corticosteroids or both (163). In addition, these patients received more blood units than the rest of the study population. Finally, CMV-specific antibody of the IgM class has been recognized as a marker of active or recent primary infection with the virus. Recent reports have shown a positive correlation between posttransfusion CMV infection and the receipt of blood from CMV IgM-positive donors (12, 63, 82). Lamberson et al. (82) also determined that a decreased incidence of TA-CMV infection occurred when only blood products negative for CMV IgM were used. However, in some instances, IgM is not detectable during reinfection with CMV and its measurement can be complicated by false-positive tests (57, 154). On the basis of a number of studies, the presence of CMV antibody to IE and E antigens may serve as an even better means of identifying infectious blood donors with active virus replication than CMV IgM (86, 95). The presence of high levels of anti-CMV E antibodies appears to reflect recent or active virus replication in the host, and the level of IgG to E antigens declines after virus excretion ceases (95). More recently, Lentz et al. (86) found that CMV-specific IgM was not consistently present in their viruric donors, but IgG antibody to E antigens correlated with viruria. In summary, direct evidence in support of an actively infected subset of infectious blood donors as a mechanism for the transmission of CMV infection has been difficult to obtain. On the other hand, the indirect evidence in support of this hypothesis is compelling and continues to increase.

Organ Transplantation

Issues regarding the mechanisms for transmission of CMV to renal transplant patients are similar in many respects to those already discussed for TA-CMV infections. Among renal transplant recipients, the incidence of CMV infection approaches 90% (27). Most reports have inferred that the importance of blood transfusions in causing CMV infections in renal transplant patients is probably low (52, 67, 101). Almost simultaneously, three investigative groups reported serologic evidence implicating the donated kidney as the transmitting vehicle for CMV infection (16, 68, 100). For example, Ho et al. (68) reported that, of 10 seronegative patients who received kidneys from seronegative donors, only 3 became infected, while of 12 seronegative patients who received a kidney from a seropositive donor, 10 became infected. However, as in TA-CMV infections, attempts to rescue virus from explants of renal parenchyma have been unsuccessful (10). A study by Naraqi et al. (101) has documented that allograft kidneys are infrequently (6%) infected with CMV. The kidney parenchyma appears to be an uncommon site of latent CMV infection and may not be the usual source of virus in patients with virurla. Only one report has suggested that CMV is easily demonstrable in renal tissue (108). In a murine kidney tissue transplantation model, kidney tissue served as an excellent source of latent virus for transmission by transplantation (59). In light of these findings, and the occasional case of primary CMV disease occurring in individuals who have lost their transplanted kidney within the first 2 weeks of transplantation, the question arises as to whether circulating cells trapped in the kidney escape after transplantation and are the source of virus (13). Nevertheless, some primary CMV infections probably result from transmission of CMV via the donor kidney. Support for this concept is the evidence clearly indicating that transplantation of kidneys from seronegative donors for seronegative recipients reduces the likelihood of primary, posttransplantation CMV infections (52).

In addition to the transplanted kidney serving as a possible source of CMV, virus may also emerge from endogenous sources in the transplant recipient coincident with immunosuppression or graft rejection (74). As discussed, CMV-seropositive recipients often shed CMV after transplantation, regardless of the serologic status of the organ donor. It has generally been assumed that, in these circumstances, these individuals reactivated their own latent virus. This assumption was substantiated in a study in mice which indicated that infections following transplantation were primarily due to reactivation of the recipient's endogenous strain (79). However, using restriction enzyme analysis, Chou (21) revealed that seropositive recipients can, in fact, be reinfected by a new CMV strain from the donor after transplantation. These data raise new issues regarding the epidemiology of CMV in transplant patients; specifically, do newly acquired viral strains also become latent in a seropositive individual, are the different CMV strains active in the same cells, and do the newly acquired CMV strains from the donor cause more symptomatic disease in seropositive recipients compared with endogenous reactivation?

Sites of Latency

It is evident from the preceding discussion that actual sites for latency, in either the blood or allograft, are unknown. Delineating the sites for CMV latency would certainly contribute to understanding the complex epidemiology of this virus. At the very least, this information would then allow for the study of CMV reactivation. The possibility of transmission or endogenous activation of CMV as a result of blood transfusion has been invoked as evidence that CMV is transmitted within transfused leukocytes. During acute infection, CMV can be isolated from buffy coat preparations (48, 74); rarely has the virus been isolated from blood of healthy blood donors (34). However, the ability of CMV to infect leukocytes has been shown. Using a two-color immunofluorescence technique with monoclonal antibodies, Rice and co-workers (129) demonstrated that CMV could infect human lymphocytes of T- and B-cell lineage, natural killer cells, and monocytes. Significantly, virus expression was limited solely to the synthesis of IE antigens in about 3% of the peripheral blood mononuclear cells. No infectious particles were visualized by electron microscopy or detected by culture. Similar findings were reported by Einhorn and Ost (40). Both studies showed that the expression of IE products was apparent only when the infecting virus was a recent clinical isolate, underscoring the significant problem of using laboratory-adapted viral strains. Similar experiences with recent CMV clinical isolates and laboratory strain AD169 have been described in subsequent studies (132, 133).

The best evidence to date that the peripheral blood mononuclear cell is a normal site of latency for CMV was provided in a study of Schrier et al. (131). Using a specific probe from the region of the CMV genome responsible for encoding the IE proteins, these investigators found that DNA from 0.5 to 2% of peripheral blood mononuclear cells from normal, asymptomatic individuals seropositive for CMV hybridized with the probe. Staining of lymphocytes with antibodies to detect the two major T-cell populations and subsequent cell sorting revealed that a higher percentage of CMV-hybridizing cells bore the OKT4 antigen (2.4%) than the OKT8 antigen (0.8%).

Recently, Gnann et al. (53) demonstrated that the main CMV-infected cells in kidneys of renal transplant patients with primary CMV infections were infiltrating inflammatory cells. Pretransplantation and serial posttransplantation renal biopsies were obtained and then studied by in situ hybridization with DNA probes representing IE and L CMV genes. All seronegative recipients studied developed primary CMV infections even though CMV nucleic acids were not detected in biopsies taken from the healthy donor kidneys before transplantation. On the basis of their data, they proposed two hypotheses to explain the acquisition of primary CMV infection in transplant recipients. The first hypothesis proposed that virus present in a small number of cells in the graft was possibly reactivated by allogeneic stimulation or immunosuppression or both and began to replicate. Subsequently, activated host lymphocytes which had infiltrated the kidney as part of the host-versus-graft response could be infected and then disseminate. The alternative hypothesis proposed that a small number of CMV donor lymphocytes or monocytes in the graft became activated, expressed virus, and then moved into the bloodstream and infected circulating host peripheral blood mononuclear cells that could later enter the graft as part of the rejection response.

However, in another study, in which CMV pathogenesis was investigated by in situ hybridization in bone marrow transplant patients, Myerson et al. (99) found CMV nucleic acid in epithelial, endothelial, stromal, and interstitial cells, but not in lymphocytes. Other possible candidates for CMV latency are epithelial cells in the salivary gland and renal tubules, as well as multiple cell types in lymphoid tissue, spleen, and bone marrow.

The transmission of CMV and the consequences of infection encompass a number of aspects of the host, of the virus and its tropisms for specific cells or tissues, and of their respective interaction (B. A. Forbes and Dock, Clin. Microbiol. Newsl. **10**:17–21, 1988). Accumulating evidence suggests that factors involved in regulating developmental processes in tissues may play a significant role in the reactivation of CMV from latency. Some factors presently under consideration for a role in reactivation are cell ploidy and its extent of differentiation, the metabolic state of the host cell, and hormonal influences (38, 50, 55, 135, 144, 149). The role antibody plays with respect to both initiation and maintenance of latency or reactivation or both is likewise unknown, as are the immunologic mechanisms related to CMV reactivation in normal individuals. Normal individuals have fluctuations over time in their complement-fixing antibody titers to CMV, suggesting a dynamic host-virus relationship (158). The cause of these variations is unknown. It has been reported that CMV-seropositive rheumatologic patients experienced reactivated CMV infection following the initiation of cyclophosphamide therapy (67). Subsequently, it was shown in the murine model that latent murine CMV could be reactivated with cyclophosphamide (89). Also, allogeneic stimulation has been implicated in the reactivation of CMV in renal transplant recipients (19, 58).

PREVENTION

The Issues

Knowledge of the epidemiology and transmission of CMV is the key to development of successful strategies for the prevention of CMV infection in the individual at high risk for serious disease. However, several features of this virus must be taken into account when considering possible strategies. One of the most notable features of CMV is its ubiquitous nature; 40 to 80% of blood donors in the United States and Europe have antibodies to CMV and therefore are infected. Moreover, most individuals who are actively infected remain asymptomatic and therefore are unaware of their carrier state. To further complicate the situation, CMV is able to establish a latent or persistent infection in host cells and can reactivate with renewed shedding of infectious virus years after primary infection (74). To date, most knowledge regarding the medical implications of viral disease stems from studies of acute viral infections. As a result of these studies, control or prevention of viral infections, such as smallpox, measles, polio, and rubella, has met with success through vaccination (137). Therefore, a virus such as CMV, which is able to establish latency and evade immune surveillance, presents particular challenges in the development of effective vaccines. Finally, a possible etiologic role for CMV in the development of human neoplastic disease has been described (41, 71, 102, 124).

Use of Seronegative Blood Products or Organs

One way to prevent CMV disease is to prevent transmission of the virus to those seronegative patients identified to be at high risk for serious, life-threatening disease. One method that has proven effective in preventing TA-CMV disease in patients, including bone marrow transplant recipients who receive massive granulocyte transfusions, is the exclusive use of CMV-seronegative blood products and organs (87, 164). This option can also be applied to organ recipients whose life is not threatened by postponing transplantation to wait for a seronegative organ (1). However, the supply of seronegative blood or organs is limited. Other approaches to prevent TA-CMV infection have involved methods to decrease the potential infectivity of seropositive units by either freezing erythrocytes (150) or extending the shelf life to provide less fresh donor blood (151); however, these methods are costly and not always appropriate. Since only a subset of seropositive donors transmit CMV infection to the recipients of their blood, studies have approached the prevention of TA-CMV disease by examining other serological markers which might better identify the infectious units of CMV-serpositive blood (2, 18, 32, 82, 86); additional studies are needed to validate the efficacy of screening donor blood for CMV IgM or possibly to early antibodies. Providing saline-washed erythrocytes or irradiated blood components has failed to prevent CMV transmission (22, 30).

A recent study of the incidence of CMV infection among 114 transfused neonates born to seronegative mothers was performed by Preiksaitis and colleagues (122) to establish the cost-benefit potential of CMV serologic screening to prevent TA-CMV infection in newborns at risk to develop serious disease. These investigators found a significantly lower incidence of CMV infection in the seronegative transfused infants than previously published data reported despite similarities in CMV antibody prevalence in the donor population, the mean number of donor exposures, and the age of the blood products used. Based on their findings, the authors argued that they could not justify providing specialized blood products for the prevention of TA-CMV infection in this particular patient population. Another concern was raised by Tegtmeier regarding the provision of CMV-screened blood products to an infant of <1,200 g whose serostatus is unknown and who requires protracted transfusion support (152). He argued that the infant could possibly be put at risk for a maternally acquired CMV infection due to the loss of passively acquired maternal antibody.

To date, the screening of blood donors for CMV antibody is the most cost-effective means of providing low-risk blood products. A future possibility may be the filtration of blood to reduce the risk of CMV transfusion to patients at high risk to develop disease (152).

Antiviral Agents

During the last four decades since the first antiviral agent, thiosemicarbazone, was described, antiviral agents selectively activated by virus-specific enzymes and which have activity against virus-specific metabolic processes without cellular toxicity have become available. For example, acyclovir has provided safe and effective treatment for herpes simplex and varicella-zoster virus infections. Unfortunately, such successful treatment for CMV disease has not yet been developed, and a few significant factors have contributed to this failure. First, no standardized methods for measuring virus susceptibility to antiviral agents exist. In conjunction with susceptibility testing of antiviral agents are the associated inherent problems of correlating in vitro data with clinical efficacy. Second, because CMV is able to establish latency and host defenses are required for viral clearance, the therapeutic value of any drug will be difficult to establish (162). Finally, because immunosuppressed patients often have diseases of multifactorial etiology and random trials have not always been performed in such patient groups, interpretation of clinical trials remains difficult. Some antiviral agents presently under evaluation for treatment of CMV disease are briefly reviewed; for an extensive review

of treatment modalities for CMV infections, the reader is referred to the excellent review by Reed and Meyers (127).

To date, clinical trials with vidarabine monohydrate, acyclovir, interferon, or different combinations of these agents for treatment of CMV disease have been, for the most part, disappointing (44). However, in a recent study, Meyers et al. (94) concluded that prophylaxis with intravenous acyclovir significantly reduced the risk of both CMV infection and CMV disease in seropositive patients after bone marrow transplantation; furthermore, acyclovir prophylaxis appeared to be associated with significantly improved survival. Acyclovir has activity against CMV strains in vitro but is much less potent than its derivative, 9-[(2-hydroxy-1(hydroxymethyl)ethoxy)-methyl]guanine, now named ganciclovir (87, 156). Opportunistic CMV infection is a serious complication of AIDS. Recently, Jacobson and Mills (73) reviewed the experience of treating various CMV infections in this patient population. To date, it appears that ganciclovir halts the progression of CMV retinitis and gastrointestinal disease; however, relapse is common once therapy is discontinued. Most clinical evaluations of ganciclovir have been nonrandomized trials. In bone marrow transplant patients, responses to ganciclovir therapy for gastrointestinal disease have been similar to those of AIDS patients, but somewhat disappointing results have been obtained for treatment of CMV pneumonia (23). Results of an uncontrolled study by Erice et al. (44), however, were in marked contrast; improvement was observed during therapy in 45% of 11 bone marrow patients and in all renal transplant recipients with CMV pneumonitis. In another uncontrolled study, two of four renal transplant patients recovered from severe CMV pneumonia, again suggesting that ganciclovir may have therapeutic applications in certain patient populations (62).

Another antiviral agent undergoing clinical trials is phosphonoformate (Foscarnet). Treatment of CMV pneumonia in bone marrow transplant patients did not improve survival despite the inhibition of virus excretion (8); however, some improvement was seen in patients with less severe CMV disease and in renal transplant patients with pneumonia. Farthing et al. (46) also described an improvement in AIDS patients with CMV pneumonitis who were treated with Foscarnet. Foscarnet also appears to show promise in the treatment of CMV retinitis in AIDS patients and might prove to be an alternative to acyclovir (157). Finally, a number of other agents are under investigation for possible antiviral activity. These include monensin, an antibiotic from *Streptomyces cinnamonensis*, and pyrrol(2,3*d*) pyrimidine nucleosides, which have been reported to be inhibitory for CMV replication in vitro (76, 155). Interference with the synthesis of the 72-kilodalton IE protein affects subsequent gene expression. The development of an antiviral agent that would interfere with the function of this predominant IE protein might inhibit viral replication and thus have the potential to serve as an effective antiviral agent (146).

Because of the disappointing clinical results obtained with antiviral chemotherapy, recent attention has focused on the role of antibody against CMV. Although it is well known that cellular immunity plays an important part in the control of CMV infections, there is increasing evidence that CMV antibody may protect against CMV disease in certain populations (25, 93, 164). In a multi-institutional, randomized, controlled trial, Snydman et al. (136) concluded that intravenously administered CMV hyperimmune globulin provides effective prophylaxis in renal transplant recipients at risk for primary CMV disease. Other recent reports have described similar success, using various immunoglobulin preparations for treating CMV infections in bone marrow transplant recipients (125) and burn patients (97). Of note, concomitant administration of ganciclovir and CMV immunoglobulin was recently reported to be associated with clearance of CMV and improved survival in allogeneic bone marrow transplant patients (43, 126). Reed et al. reported a significantly better survival rate for those patients who received this treatment modality compared with those who received antiviral agents alone; in addition, viral excretion ceased in 74% of these patients who had been treated for more than 96 h.

Vaccination

A live attenuated vaccine has been developed and used in preliminary clinical trials in renal transplant patients. However, possible benefits and risks of a general vaccine program for preventing congenital CMV infections require further study due to the ability of CMV to cause latent infections and its possible oncogenic potential. Therefore, for the present, targeted populations are those patients identified to be at high risk to develop serious CMV disease.

The use of live attenuated virus vaccine is under active investigation (42, 51, 119–121). The Towne strain of CMV, maintained for 125 passages in cell culture by Plotkin and co-workers (51, 119, 121), has been shown to be nonvirulent for healthy individuals and renal transplant recipients and to induce cellular and humoral immunity. Glazer et al. (51) reported that reactivation of the vaccine virus was not detected in 12 seronegative vaccinees who later had renal transplants. Attenuation and nonvirulence of the Towne strain vaccine were subsequently confirmed by Quinnan et al. (123). Furthermore, restriction enzyme analysis of CMV strains isolated during a study of Towne strain live vaccine in renal transplant patients revealed that such strains were not identical to the vaccine strain; thus, Plotkin concluded that the vaccine strain did not appear to induce latency (118).

However, the development of the vaccine is not without problems. First, the oncogenic potential of CMV must still be taken into consideration with any vaccine program. Second, the great structural variability of infecting CMV strains must also be considered since this variability could pose significant obstacles in the development of effective vaccines. Last, because immunization is a potential means of controlling CMV infection and preventing its effects, the extent and consequences of reinfection with new strains of CMV in previously immune persons must also be taken into account.

FINAL COMMENTS

CMV is a ubiquitous DNA virus which infects humans, often becomes latent, and reactivates under certain circumstances. For the most part, CMV infection does not result in clinically significant disease for immunocompetent individuals; however, it can cause significant disease in certain immunocompromised patients. Its ubiquity coupled with a complex natural history in which it exists in a dynamic relationship with its human host present significant challenges for developing strategies for the prevention of CMV infection in those patients at risk to develop life-threatening disease. A thorough understanding of the viral epidemiology is a prerequisite if CMV infection is to be prevented. As evident in the preceding discussion, major gaps exist in our

understanding of how this virus is acquired. Despite the numerous unanswered questions, major advances have still been made in understanding both CMV transmission and disease prevention.

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