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Cytomegalovirus Infection After Liver Transplantation: Clinical Manifestations and Strategies for Prevention

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Cytomegalovirus (CMV) has been shown to be an important pathogen in liver transplant recipients. The presence of primary infection and the use of OKT3 monoclonal antibodies appear to be risk factors for symptomatic infection. In my experience, the disease is clinically similar to the CMV disease seen in other transplant groups except that infection of the liver may be clinically more important in liver recipients than in other transplant recipients. Various regimens for prevention of CMV infection in transplant recipients have been investigated, including vaccination, prophylaxis with a variety of polyclonal immunoglobulin preparations, the use of immunomodulators such as interferon-α, and antiviral prophylaxis with acyclovir. These studies have been performed in kidney or bone marrow recipients and may not be applicable to liver recipients. Studies in progress on which no data are currently available employ human monoclonal immunoglobulin and ganciclovir. It is not possible at present to make any specific recommendations for prophylaxis. It is likely that ongoing randomized studies and further understanding of host–virus interactions in CMV disease will lead to useful prophylactic regimens in this group of patients.

Shortly after cytotoxic drugs were introduced for the clinical management of kidney transplant recipients, cytomegalovirus (CMV) was found to be a cause of serious and sometimes fatal illness [1, 2]. Subsequently, the importance of this pathogen in clinical heart, lung, and bone marrow transplantation also was recognized and carefully investigated [3–7]. Although cases of CMV disease were also recognized in liver recipients during the early, exploratory years of liver transplantation, these were overshadowed by the high frequency of infections with bacterial and fungal agents [8].

Since the introduction of cyclosporine, liver transplantation has become an accepted treatment of end-stage liver disease, and it is now practiced at many centers in the United States and throughout the world [9, 10]. With this expansion in clinical activity has come a parallel growth in research, and a number of articles have now appeared that document the importance of CMV as a pathogen in liver recipients. This article reports on some of these findings and discusses strategies of treatment and prevention of CMV disease in liver recipients. Since virtually no direct information is available on therapeutic or prophylactic strategies in liver recipients, this latter discussion will, of necessity, deal with information from studies in kidney and bone marrow recipients and will attempt to focus on the applicability of these data to liver recipients.

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CMV Infection After Liver Transplantation

The initial studies of infections in cyclosporine-treated transplant recipients from the University of Pittsburgh showed that the rate of CMV infection in liver recipients was similar to that in kidney and heart transplant recipients [11, 12]. The rate of symptomatic CMV infection in liver recipients, however, was considerably higher (32% vs. 8%) than that in kidney recipients, although it was similar to that in heart recipients (34%). Although the number of patients studied was small, the results were particularly useful because at that time the patient groups studied were on very similar regimens of cyclosporine and prednisone for immunosuppression; azathioprine and anti-T cell globulins were not in use.

In those early studies, the individual transplant populations were too small to permit the exploration in any depth of the importance of factors such as the role of primary vs. reactivation infection in the production of CMV disease, the importance of the donor organ in the transmission of CMV, or

the impact of the immunosuppressive regimen on outcome.

A few years later, studies were undertaken to analyze infectious complications in adult recipients of liver transplants in greater detail. The first such study examined all infectious complications in a well-defined population of adult liver transplant recipients who had been followed prospectively [13]. By the time of that study (1984–1985), a number of important changes in the management of these patients had taken place. The most important of these changes was the introduction of the monitoring of cyclosporine serum levels and the subsequent general lowering of cyclosporine doses in this population. At the same time, immunosuppressive regimens had become more varied. OKT3 monoclonal antibodies had been introduced for the treatment of rejection not responsive to steroids, and some patients also received courses of azathioprine, primarily to enable further reduction in cyclosporine doses when nephrotoxicity was encountered. In that study, CMV was found to be the most frequent cause of severe infection—22 cases in the 101 patients. It was not, however, the most important cause of death due to infection. Fungal infections and various types of intraabdominal bacterial infections caused more deaths. Nonetheless, five of 26 deaths in the population were linked to serious tissue-invasive CMV infection. Typical clinical findings in liver recipients with CMV disease were fever, neutropenia, thrombocytopenia, and atypical lymphocytosis, findings similar to those in kidney and heart recipients with CMV disease [3–7]. Because at that time invasive techniques were not frequently used to diagnose CMV disease, tissue-invasive disease was most frequently found on postmortem examination. The symptomatic infections peaked during the second posttransplant month, and all but one occurred in the first 7 weeks after initial or repeat transplantation.

To further characterize the manifestations and timing of CMV infection in liver recipients and analyze risk factors for the occurrence of severe and fatal infections, my colleagues and I then studied 93 consecutive liver recipients for whom pretransplant CMV serologic data and adequate posttransplant follow-up information were available [14]. The rates of CMV infection and disease found in that study are shown in table 1 and are analyzed according to the patients' pretransplant CMV serologic status. The data show an overall infection rate of 59%, a figure that is in the same range or slightly lower than previous estimates in kidney and heart transplant recipients [6, 7, 15]. Forty-nine percent of infected patients developed CMV disease. Almost all patients with primary infection developed symptoms, and 29% developed disseminated disease. All six cases of disseminated disease occurred in patients who had received OKT3 monoclonal antibodies for the treatment of rejection, and the rate of disseminated infection appeared particularly high (five of nine; 55%) in those patients who received OKT3 while experiencing primary infection. That study not only demonstrates the importance of CMV infection in this population but also identifies important subgroups of patients for possible prophylactic intervention.

The organ donor has previously been implicated as an important source of CMV infection in kidney and heart transplant recipients [6, 16]. The data from the Pittsburgh study of the transmission of CMV infection by the liver donor demonstrate a clear relationship between the implantation of a liver from a seropositive donor and the development of primary infection in a CMV-seronegative recipient (table 2). The donor CMV status did not appear to affect the frequency of infection in CMV-seropositive recipients. Previously published data from the Mayo Clinic also suggested the importance of the organ donor as a source of CMV infection in liver recipients [17]. At that center, however, seronegative recipients generally received seronegative blood products.

Table 1. Frequency of CMV infection and disease after liver transplantation.

CMV serologic status before transplantation	No. of patients	No. of CMV infections (% of patients)	No. of symptomatic CMV infections (% of infections)	No. of disseminated CMV infections (% of infections)
Seronegative	37	17 (46)	15 (88)*	5 (29)*
Seropositive	56	38 (68)	12 (32)*	1 (3)*
Total	93	55 (59)	27 (49)	6 (11)

NOTE. Table is adapted from Singh et al. [14].

* $P < .01$; seronegative vs. seropositive.

Table 2. CMV infection rates according to serologic status of patients and their organ donors.

Recipient CMV serologic status before transplantation	Donor CMV serologic status/ no. of recipients (%)	
	Seropositive	Seronegative
Seronegative	13/14 (93)*	1/12 (8)*
Seropositive	15/21 (71)	11/14 (79)

NOTE. Table is adapted from Singh et al. [14].
* $P < .001$.

Adult liver recipients in the study conducted in Pittsburgh received about 20 units of unscreened red blood cells and 20 units of unscreened platelets during and after transplantation [18]. Thus, the low (8%) rate of CMV infection in the seronegative liver recipients who received seronegative organs suggests that the provision of CMV-seronegative blood products would not have a substantial impact on the incidence of primary CMV infection in adult liver transplant recipients. Data from other centers will have to be examined to ascertain whether this is a generalized phenomenon. A previous study of heart and heart-lung recipients who underwent transplantation in Pittsburgh between 1981 and 1983 showed that the majority of primary infections occurred in recipients of organs from seronegative donors, a finding implicating other factors, such as the use of unscreened blood products, as the source of the infections [7]. It is not known if the discordant findings in these different organ transplant groups in Pittsburgh are related to intrinsic differences in the types of organ transplantation, to alterations in blood-banking practices in the last few years, or to other factors.

In 55 adult liver recipients, the median onset of infection was 28 days, with a broad range of 2 weeks to >5 months (figure 1, *left*). The later infections were mostly reactivation infections and often followed a second transplant operation. The timing of primary and reactivation infections did not differ significantly. Symptomatic disease was subdivided into CMV syndromes, local CMV disease such as CMV gastritis or CMV hepatitis, and disseminated CMV. The median onset of CMV disease in 27 liver recipients was 43 days after transplantation or, on the average, 2 weeks after the onset of viral shedding (figure 1, *right*). The timing of the different types of CMV disease did not differ significantly. Notably, though, all cases of disseminated CMV disease occurred during the first 3 months after transplantation.

Biochemical evidence of hepatitis due to CMV frequently is seen in transplant recipients with CMV infection. In liver recipients, however, CMV hepatitis is difficult to diagnose without biopsy of the liver because of the many competing sources of liver injury, such as rejection or cholangitis. During the early years of the Pittsburgh liver transplant program, few biopsies were done and thus CMV hepatitis was usually diagnosed either at autopsy or retransplantation of the liver [19]. Since 1986, biopsy of the liver has increasingly been used for diagnosis of rejection and

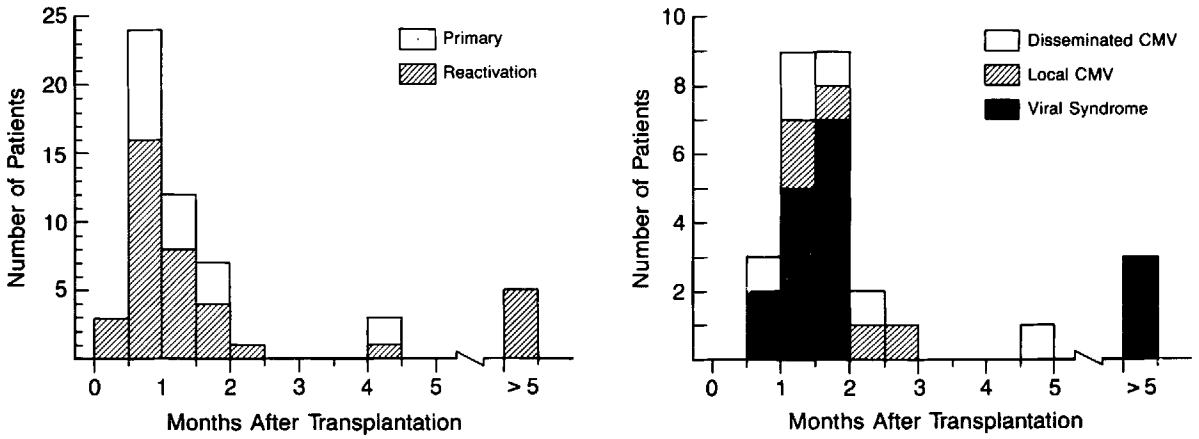

Figure 1. *Left*: Timing of primary and reactivated CMV infections after liver transplantation, by onset of viral shedding or seroconversion (55 patients). *Right*: Timing of symptomatic CMV infections after liver transplantation, by onset of symptoms (27 patients).

other causes of liver dysfunction after transplantation. An index of the importance of CMV hepatitis can be derived from my recent experience with the use of ganciclovir. Over a 12-month period from September 1987 to September 1988, 57 adult liver recipients were treated with ganciclovir for tissue-invasive CMV infection on a compassionate-release protocol. This represented 17% of the 326 adults who received liver transplants during the same interval. Thirty-eight (67%) of these had biopsy-proven evidence of CMV hepatitis—usually inclusion bodies. Seventeen of these patients also showed evidence of invasive disease in the lung or bowel. It is interesting that the overall mortality among the 38 patients who had CMV hepatitis was significantly lower than that among the 19 patients who had invasive disease in other organs but no documentation of CMV hepatitis (16% vs. 43%; $P < .05$, χ^2). Since only a few of these patients died of CMV disease, the meaning of this finding is not clear. It may, however, reflect a benefit of early diagnosis, since liver biopsies were routinely carried out by the transplant team and did not require consultation of other services for endoscopy, bronchoalveolar lavage, or lung biopsy.

The pathology of CMV infection in the transplanted liver has been described by Demetris et al. [20]. The usual finding is microabscesses or microgranulomata scattered around the liver lobule. Some patients have an infiltrate of chronic inflammatory cells in the portal area. The frequency of inclusion bodies is extremely variable. Clinically, the disease may be mild and self-limited, as in other transplant recipients, but cases that are fatal or require retransplantation have also been described [19].

The mortality associated with CMV infection in liver recipients is difficult to determine with accuracy because of the presence of coexisting diseases. In two studies at the University of Pittsburgh, CMV infection was associated with a fatal outcome in ~5% of the total population, or ~10% of the infected patients [13, 14]. Whether CMV infection is a cofactor in morbidity from bacterial and fungal diseases in these patients as has been suggested for heart and kidney transplant recipients is a subject for future study [21, 22].

It is apparent that CMV infection in liver transplant recipients shares many characteristics with CMV infection in other solid organ transplant recipients. These include transmission by the transplanted organ, similar clinical manifestations and timing, and association of symptomatic disease with primary infection and possibly the use of anti-T cell globulins [3–7, 23–25]. Probable differences are a potentially greater severity of liver involvement and a high ratio of symptomatic disease to asymptomatic disease.

Table 3. Strategies for the prevention of CMV disease after organ transplantation.

Avoidance of infection
Donor selection
Blood-product screening
Active immunization
Immunoglobulin prophylaxis
Immunomodulation
Specific antiviral prophylaxis

Strategies for Prevention or Modification of CMV Disease

The scientific literature pertaining directly to the prevention or modification of CMV disease after liver transplantation is scant. It is likely—but not certain—that data collected in other transplant groups will be partly or even largely relevant to liver transplantation. The following discussion will deal with prophylactic trials in other transplant groups and will attempt to assess their applicability to liver transplantation. Table 3 lists the approaches to the reduction of CMV disease after liver transplantation that have been studied.

Donor Selection

Since primary CMV infections are more likely to produce morbidity than are reactivation infections and the donor organ is a demonstrated source of virus, matching of donor and recipient by serologic status is a feasible way of decreasing the overall frequency of illness due to CMV in a population of transplant recipients. Such a program has been reported in kidney transplantation [26]. Logistic difficulties make this approach more complicated in heart and liver transplantation, but since donors are now tested for antibodies to human immunodeficiency virus and hepatitis B surface antigen, it should be feasible to determine their CMV serologic status in a timely fashion—given the availability of relatively rapid and accurate tests for CMV antibodies, such as latex agglutination [27]. However, constraints on the transplantability of organs may not be popular with some transplant surgeons. Also, superinfection with do-

nor strains of virus may occur in CMV-seropositive recipients, and some centers have reported a higher rate of CMV morbidity in seropositive recipients receiving seropositive organs [28–30]. Nonetheless, this maneuver is an administrative rather than a pharmacologic intervention and should be inexpensive compared with drug therapy; it thus deserves further study.

Blood-Product Screening

Numerous data demonstrate that CMV may be transmitted by blood products, although estimates of risk per unit of blood vary widely and the risk of CMV infection with blood transfusion may be declining [15, 31]. Provision of seronegative blood products to liver recipients presents a formidable problem for a large transplant center because of the large number of units of blood that must be tested. Some centers provide screened blood products at least to a preset limit [17]. Because the rate of CMV infection in seronegative adult recipients at the University of Pittsburgh is low if they receive an organ from a seronegative donor, I believe the provision of seronegative blood products to adult liver recipients is not justified at this time. Other centers may have higher rates of CMV infection related to blood products, and further study is desirable.

Active Immunization

In theory, one of the simplest interventions for prevention of CMV disease after transplantation would be immunization of seronegative recipients. A candidate vaccine, developed from the Towne strain of virus, has been developed and extensively tested. Immunization with this vaccine has been shown to produce seroconversion in healthy subjects and in most kidney transplant candidates, with acceptable adverse effects [32]. Reactivation of the vaccine strain could not be demonstrated in vaccine recipients after transplantation [33]. Unfortunately, studies of this vaccine in clinical transplantation have so far not shown a definite benefit. In one controlled study, 24% of the seronegative transplant candidates failed to produce antibodies after immunization [34]. The frequencies of CMV infection and disease were not lowered in seronegative recipients who received donor organs from seropositive donors, although their overall morbidity from CMV infection was less than that in controls. A second, larger study of 236 transplant recipients at the University of Minnesota also found a 24% failure of seroconversion in 63 vaccinated seronegative recipients [35]. No difference was found in the rates of CMV infection and disease in vaccine and placebo recipients. Research into CMV vaccines, particularly subunit vaccines, is continuing [36]. Although it is not likely that complete protection against CMV infection will ever be afforded by a vaccine because of the strong cell association of the virus, a product that provided even partial protection against serious manifestations of CMV disease would be a useful adjunct in liver transplantation.

Immunomodulation

Since serious CMV infections occur primarily in clinical conditions associated with depressed cellular immunity, attempts to bolster cellular antiviral immunity would seem to be a rational approach to prophylaxis. Interferon-α has been the only immunomodulator studied in detail. In one trial, kidney transplant recipients who received Cantell leukocyte interferon (3×10^6 units) two to three times a week for 14 weeks after transplantation experienced a lower frequency of CMV syndromes than did placebo recipients despite similar infection rates [37]. By contrast, interferon was not found to be of any benefit in preventing CMV disease after marrow transplantation [38]. The major adverse effects of treatment have been neutropenia, thrombocytopenia, and fatigue. Enthusiasm for the use of interferon seems to be waning, possibly because of reports of steroid-resistant rejection in kidney transplant recipients receiving recombinant interferon [39]. Liver transplant recipients seem to be poor candidates for interferon trials because of the drug's mild hepatotoxicity and its requirement for intramuscular administration [40]. Because of the ever-present risk of rejection, serious consideration of risks and benefits should be made before administering immunomodulators to transplant recipients.

Passive Immunization with Immunoglobulins

Interest in the use of human immunoglobulins to protect against CMV infection after transplantation has paralleled the development of preparations that can be safely administered intravenously in large quantities. In the last 10 years, a number of placebo-controlled studies have addressed the issue of

whether plasma or immunoglobulin with substantial titers of antibodies to CMV can protect transplant recipients against CMV infection [41–46]. In the largest of these studies, 38 bone marrow transplant recipients who received 1 g of commercially available immunoglobulin before transplantation and at weekly intervals until 120 days after transplantation [45] were compared with 37 placebo-treated controls. CMV infection occurred at similar rates in treated and control groups, but the treatment group experienced a significant reduction in the frequency of symptomatic CMV infection (21% vs. 46%) and interstitial pneumonia (18% vs. 46%). The therapy was generally well tolerated. A recent multicenter study of kidney transplant recipients employed a hyperimmune CMV immunoglobulin preparation and studied 59 CMV-seronegative recipients of organs from seropositive donors [46]. The cumulative dose of hyperimmunoglobulin given during the entire treatment interval was only 550 mg/kg. That study found a significant reduction in symptomatic illness due to CMV (21% from 60%) and in the incidence of fungal or parasitic opportunistic infections (0% from 20%) in globulin recipients. No difference was found in the frequency or timing of CMV infection as measured by virus isolation.

Most of the controlled studies cited above support the concept that prophylactic immunoglobulin therapy can attenuate the severity of CMV disease after transplantation. One major exception is a study from the Seattle bone marrow transplant group that did not demonstrate any benefit of intravenous γ-globulin prophylaxis in the prevention of CMV infection or disease [44]. That study used a higher dose of the same immunoglobulin preparation used in the kidney transplant study mentioned above, so that the failure to show any benefit cannot be attributed to the preparation used.

Intravenous immunoglobulin therapy appears to have low toxicity [44–46]. It is quite expensive, and the protection shown against CMV disease is only partial. Also, there is little uniformity among studies as to dosage, interval of treatment, or the preparation employed. The applicability of the kidney and bone marrow transplant studies to liver transplantation is unclear and needs to be demonstrated. More information is needed on the nature of the active moiety in these preparations so that they can be compared and progress can be made toward developing rational and cost-effective treatment strategies. Until now it has been unclear whether neutralizing antibodies, antibodies mediating antibody-directed cellular cytotoxicity, or other types of antibodies in these polyclonal products are the essential ingredients. With the development of human monoclonal antibodies, it should be possible to determine in clinical studies which antibodies, if any, provide protection, with a precision down to the epitope recognized by the antibody [47].

Antiviral Therapy

The success of acyclovir in treating herpes simplex and herpes zoster infections in immunocompromised individuals represents a triumph of specific antiviral chemotherapy [48, 49]. Unfortunately, acyclovir has much less activity against CMV, and the results of treatment of CMV infections in transplant recipients have been disappointing [50–52]. Adenine arabinoside is an older agent that has also been extensively studied. It does not appear to be sufficiently active against CMV and produces both neutropenia and neurotoxicity [53].

Recently it has become clear that acyclovir may be successful prophylactically despite its failure therapeutically. The first indication of this came from a study of bone marrow transplant recipients who received high doses of intravenous acyclovir for 30 days after transplantation to protect against cutaneous and invasive herpes simplex infections [54]. This group had significantly less invasive CMV disease than did a control group who did not receive acyclovir because they were seronegative for herpes simplex. This study has now been followed by a well-done, prospective, randomized, and placebo-controlled trial of high-dose oral acyclovir in kidney transplant recipients that shows a significant (70%) reduction in CMV disease in the treatment arm [55]. In that study, acyclovir was administered orally at doses of 3,200 mg/d for 3 months after transplantation. Although these doses are considerably larger than those usually administered, they were generally well tolerated. If these results can be confirmed and extended to other transplant groups, prophylactic oral acyclovir could well become a standard of care in transplantation.

At present the most promising new drug is ganciclovir. This compound has excellent antiviral activity against CMV both in vitro and in vivo [56–58]. No controlled studies—either prophylactic or therapeutic—have been reported, and conclusions have to be drawn from series of patients treated on a

compassionate-release basis. In a small study of bone marrow recipients with CMV pneumonia, the drug had antiviral activity, but nine of 10 patients died [58]. Reports of therapy in solid organ transplant recipients have been more encouraging [59–62]. In one study, six of eight heart or heart–lung transplant recipients with severe CMV infections improved with therapy, and all responded with clearing of virus [60]. Another study found improvement in nine of 10 liver or kidney transplant recipients with tissue-invasive CMV disease treated with ganciclovir [62]. Ganciclovir is more toxic than acyclovir; the major adverse effects are neutropenia and thrombocytopenia, and little is known about long-term adverse effects [58, 61]. Whether adverse effects will ultimately preclude its use as a prophylactic agent cannot be determined at present. The need for frequent intravenous dosing would also make prophylactic use of the drug cumbersome in those transplant recipients who are able to leave the hospital within a few weeks of transplantation.

Another antiviral agent active against CMV is foscarnet (phosphonoformate). The compound appears to show activity in the treatment of CMV retinitis in patients with AIDS [63]. Significant nephrotoxicity was encountered in some patients, and more data are needed before the agent can be recommended for investigative trials in transplant recipients receiving cyclosporine.

The Pittsburgh Immunoglobulin Trial

Previous research on CMV infections in the Pittsburgh liver transplant population has been largely descriptive. It is likely that future research will be more interventional. Currently, the Department of Surgery at the University of Pittsburgh, in cooperation with the Department of Surgery at the Baylor University Medical Center in Dallas, is conducting a two-center, placebo-controlled, double-blind study of the prophylactic effect of a commercial intravenous immunoglobulin preparation (Sandoglobulin; Sandoz, East Hanover, N.J.) against CMV infection. It is anticipated that 200 patients will be enrolled in the study—150 of them in Pittsburgh. Enrollees will receive either immunoglobulin (500 mg/kg) or placebo as an intravenous infusion shortly after liver transplantation, then weekly for 4 weeks, and finally every 2 weeks for the subsequent 8 weeks. The total dose of immunoglobulin administered will be 4.5 g/kg. Placebo recipients will receive albumin. Although the major endpoint of the study is the development of tissue-invasive CMV infection, the study also is designed to gauge the effect of the immunoglobulin on the occurrence and outcome of the major pyogenic infections that are a significant problem after liver transplantation. Because intravenous immunoglobulin is expensive, I am also collecting information on certain indices of hospital morbidity, such as days spent in the hospital, days spent in the intensive care unit, days of fever, and days receiving intravenous antibiotics to estimate any cost savings (or losses) that might occur with the use of this product.

Conclusion

CMV is an important pathogen in liver transplant recipients, and an attempt to prevent or favorably modify CMV infection in these patients is warranted. Since no direct data are available on effective prophylactic strategies after liver transplantation, these data must be collected before firm recommendations can be made. In the interim, for individual liver transplant groups, one may elect to extrapolate from studies performed in other transplant groups and institute or study one or more of the strategies outlined above. In doing this one should pay particular attention to the potential benefit, toxicity, and cost of the individual regimens, with a realization that CMV infection is an investigative as well as a clinical problem in transplantation. It is likely that emerging technologic advances, such as monoclonal antibodies and specific antiviral agents, will play an increasing role in these investigations in the next few years.

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