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Infections with Cytomegalovirus and Other Herpesviruses in 121 Liver Transplant Recipients: Transmission by Donated Organ and the Effect of OKT3 Antibodies

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One hundred twenty-one adult liver transplant recipients were studied for the incidence, risk factors, and morbidity associated with herpesviruses infections after transplantation. The overall incidence of infection was 59% for cytomegalovirus (CMV), 35% for herpes simplex virus (HSV), 25% for Epstein-Barr virus (EBV), and 7% for varicella-zoster virus (VZV). Primary CMV infection occurred in 46% and reactivation CMV infection in 67% of the susceptible recipients. Symptomatic and disseminated CMV diseases were more common when patients developed primary infection ($P < .01$, for both comparisons). The donor organ appeared to be the only important source of CMV infection in seronegative recipients. The use of OKT3 antibodies was associated with disseminated CMV disease in patients with primary infection ($P = .04$) but not with reactivation infection ($P > .10$). Although most HSV infections were oral or genital reactivations, three cases of HSV hepatitis occurred—one was a primary infection. Symptomatic reactivations of HSV were observed in 53% of HSV-seropositive recipients who received OKT3, versus 31% of seropositive recipients who did not receive OKT3 ($P = .05$).

Infections with cytomegalovirus (CMV) and other herpesviruses are a major source of morbidity and mortality after organ transplantation [1]. Of all the herpesviruses, CMV is the agent most often associated with severe disease or death [2]. A number of factors contribute to the severity of CMV infection in transplant recipients. Primary infection as opposed to reactivation infection with the virus [2, 3] and the use of immunosuppressive regimens containing anti-thymocyte globulin (ATG) appear to be associated with more-severe CMV disease [4, 5]. In addition, the type of transplant operation is an important determinant of the morbidity due to CMV. For instance, both bone marrow and heart-lung transplant recipients have higher rates of CMV pneumonia than do kidney recipients [1, 6, 7].

Our earlier studies of infections in kidney, heart, heart-lung, and liver transplant recipients in Pittsburgh showed that CMV and other herpesviruses were a significant problem in liver transplant recipients receiving cyclosporine [8]. A study of viral infections, incuding herpesvirus infections, in pediatric transplant recipients, most of whom were liver recipients, has recently appeared [9], but there still has been no comprehensive study of herpesvirus infections in adult liver transplant recipients, particularly since the initiation of routine cyclosporine monitoring in 1983. Therefore, we studied 121 consecutive adult liver transplant recipients at our institution to analyze the incidence, timing, risk factors, and clinical outcome associated with herpesviruses infections. We hoped to determine whether the hepatic allograft was a significant source of CMV infection and whether the use of newer immunosuppressive measures, such as OKT3 monoclonal antibody (Ortho Pharmaceutical, Raritan, NJ) introduced for treating liver rejection, had a measurable impact on CMV or herpes simplex virus (HSV) infection.

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Patients and Methods

Study population. The study population consisted of 121 consecutive adults who underwent orthotopic liver transplantation at our institution between January 1984 and September 1985, who survived for at least 72 h postoperatively, and on

whom preoperative serum samples were available. There were 46 men and 75 women whose average ages were 38 and 39 y, respectively. Their clinical diagnoses were primary biliary cirrhosis (35), chronic active hepatitis (24), sclerosing cholangitis (20), cryptogenic cirrhosis (10), malignancy (9), Caroli's diseases (3), drug- or alcohol-induced hepatic necrosis (5), hemochromatosis (3), Budd-Chiari syndrome (3), α-1-antitrypsin deficiency (2), Wilson's disease (2), secondary biliary cirrhosis (4), and cystic fibrosis (1). There were a total of 26 deaths. The duration of follow-up in living patients ranged from 313 to 930 d, with a median of 530 d. Clinical data regarding infections were collected by reviewing patients' records as well as by follow-up by two of the authors (N. S. and S. K.).

Immunosuppression. Standard postoperative immunosuppression consisted of cyclosporine (CsA) and corticosteroids. CsA was administered iv at a dose of 2 mg/kg per d on the day of surgery and then orally at 6 mg/kg per d after surgery. The dosage was adjusted individually to achieve a whole blood level of CsA between 800 and 1000 ng/mL, as measured by RIA. Beginning on the day of surgery, methylprednisolone was administered iv at a dose of 200 mg and tapered over five to seven days to a maintenance dose of 20 mg of methylprednisolone or oral prednisone. Rejection episodes were treated either with a "recycling" of high-dose oral steroids starting at 200 mg of prednisone and tapering to 20 mg over five days or with 1-g iv boluses of methylprednisolone. For the purpose of this study, one recycle and one bolus of steroids were considered equivalent. For more-severe degrees of rejection, OKT3 antibody was administered. Azathioprine (AZA) was usually added to the immunosuppressive regimen to reduce CsA dosage in patients experiencing nephrotoxicity. AZA was administered orally at a dose of 1–2 mg/kg, and OKT3 was administered iv at a dose of 5 mL daily and continued for seven to 14 days. Mean monthly CsA levels for the first three months postoperatively were determined from the monthly means of each patient's weekly median levels of CsA.

Laboratory follow-up. Preoperative serum samples from all transplant recipients were analyzed for antibodies to CMV, Epstein-Barr virus (EBV), and HSV. A semiautomated immunofluorescent test (FIAX®; International Diagnostic Technology, San Jose, Calif) was used for testing antibodies to CMV and HSV, and titers of ⩾30 and ⩾12, respectively, were considered positive. All equivocal CMV FIAX results were checked with an anticomplement immunofluorescence test (ACIF), and titers of ⩾1:4 were considered positive [10]. Ordinarily, a positive postoperative culture for CMV was considered adequate for diagnosing CMV infection [2, 11]. In the absence of positive CMV cultures, postoperative sera were also assayed for CMV antibodies by ACIF. Antibodies to EBV viral capsid antigen (VCA) and early antigen (EA) were determined on preoperative and postoperative sera by standard immunofluorescence, and titers ⩾1:5 were considered positive [12]. Significant antibody rises (greater than fourfold) were were confirmed by simultaneous assay. In addition, throat washes and urine and buffy coat samples were obtained from recipients every two to four weeks postoperatively and cultured for CMV [8].

One patient with no detectable HSV antibodies before transplantation developed HSV hepatitis after transplantation. Serum samples from this recipient and donor were analyzed for HSV type-specific antibodies by an immunodot enzymatic assay [13, 14]. Briefly, HSV type 1-specific glycoprotein (gG-1) and HSV type 2-specific glycoprotein (gG-2) were prepared as described by Lee et al. [13, 14] and used as antigen in an immunodot assay on small disks of nitrocellulose membrane in 96-well plates. The sera were tested at a 1:50 dilution, and serum controls were used for each assay.

CMV infection and disease. Primary infection was defined by isolation of virus or by seroconversion in a patient who was seronegative before transplant surgery. Reactivation infection was diagnosed by either a fourfold or greater rise in antibody titers compared with pretransplant levels by ACIF or by isolation of virus in a seropositive recipient. Twenty-eight patients did not have postoperative CMV cultures or sera available for antibodies testing and were therefore excluded from analysis of CMV infections; 93 patients then remained for evaluation. To exclude the effect of passively transferred antibodies from blood transfusion during surgery, we only used sera collected >30 d after transplantation to document rises in antibody titer. Clinical diseases caused by CMV infection were the following types: viral syndrome, localized CMV disease, and disseminated CMV disease. Viral syndrome due to CMV required the following: (*1*) laboratory evidence of CMV infection, as defined above; (*2*) fever ⩾38 C for at least one week and no other source to account for it; and (*3*) one of the following findings—atypical lympho-

cytes ≥3%; white blood cell count ≤4000/mm³; and platelets ≤100 000/mm³. Localized CMV disease was defined as tissue invasion of a single organ determined histopathologically and/or by culture of virus from tissue. Disseminated CMV disease was defined as tissue involvement of two or more noncontiguous sites.

EBV infection. EBV infection was defined by a fourfold or greater rise in IgG antibody titers against VCA occurring > 30 d after transplantation. Thirty-four of 121 patients were excluded from analysis of EBV infection because of a lack of appropriate postoperative sera, and 87 assessable patients then remained. Patients were defined as having a symptomatic EBV infection if they had either a febrile viral syndrome defined the same way as for CMV, but with no laboratory evidence of CMV infection, and a fourfold or greater rise in IgG VCA titers to EBV. We defined EBV-associated lymphoproliferative lesions by the presence of EBV DNA in tissues by using nucleic acid hybridization and/or by the presence of EBV nuclear antigen by using immunofluorescent staining [12].

HSV and VZV infections. HSV infection was defined as the presence of typical symptomatic oral or genital ulcers. For atypical lesions or those outside the genital or oral area, isolation of virus or typical viral cytopathology was also required.

VZV infection was determined clinically by the presence of typical dermatomal lesions. In one patient with clinical varicella the virus was cultured from skin lesions and blood, and the patient's pretransplant serological status was determined by an indirect fluorescent-antibody test (Electro-Nucleonics, Columbia, Mass).

Statistical methods. Observed proportions were compared using the χ^2 test or, if the numbers were small, Fisher's two-tailed exact test. Calculated means were compared using Student's t test. Differences were considered significant at $P < .05$.

Results

CMV infection. Fifty-five (59%) of 93 patients developed CMV infection. These included 17 (46%) of 37 seronegative recipients and 38 (67%) of 56 seropositive patients (table 1). Fifteen (88%) of 17 recipients with primary infection had symptomatic disease. Seven patients had a viral syndrome, three patients had localized CMV infection, and five patients had disseminated CMV infection. Two cases of localized CMV involved the lung, and one involved the small bowel. In the latter case, the diagnosis was made by endoscopic biopsy through an ileostomy. Of the five patients with disseminated CMV, three died, and multiple organ involvement was found at autopsy. Two patients with disseminated CMV disease (one with hepatitis and pneumonitis and the other with hepatitis and duodenitis) recovered.

Symptomatic CMV disease was diagnosed in 12 (32%) of 38 patients with reactivated CMV infection and was significantly less frequent than after primary infection ($P < .01$). Nine patients had a benign viral syndrome, two patients had localized CMV infection (one with hepatitis and one with pneumonitis), and one patient had disseminated CMV. Disseminated CMV infection occurred less often in patients with reactivation infection (one of 38) compared with patients with primary CMV infection (five of 17; $P < .01$).

Mortality. Of the 55 infected patients, 12 (22%) died. This rate was higher than, but not significantly different from, the 8% (three of 38) mortality rate found in uninfected patients ($P = .12$). Also, mortality in patients with symptomatic CMV infection

Table 1. Frequency of CMV infection and symptomatic disease in liver transplant recipients.

Preop CMV serology	No. of assessable patients	No. of patients with				Total no. of symptomatic patients (%)
		Infection (%)	Viral syndrome	Localized CMV	Disseminated CMV	
Negative	37	17 (46)	7	3	5*	15* (88)
Positive	56	38 (67)	9	2	1*	12* (32)
Total	93	55 (59)	16	5	6	27 (49)

NOTE. Preop = preoperative.

* $P < .01$ for patients with primary infection compared with patients with reactivation infection who developed symptomatic CMV disease and with patients with disseminated CMV disease ($P < .01$ for both comparisons).

Table 2. Relation of CMV infection to blood products transfused.

Blood product (mean units transfused)	Seronegative recipients*		Seropositive recipients*	
	Primary infection (n = 17)	Not infected (n = 20)	Reactivation infection (n = 38)	Not infected (n = 18)
Red blood cells	29	26	45	27
Fresh frozen plasma	32	33	52	34
Cryoprecipitate	16	9	13	14
Platelets	44	32	61	34
Total units	121	100	171	109

*No significant differences were found between the number of units of red blood cells, fresh frozen plasma, cryoprecipitate, platelets, or total blood product units for infected vs. uninfected patients ($P > .1$).

was 18% (five of 27) and did not differ from the 25% (seven of 28) mortality rate found in patients without symptomatic CMV infection. The mortality rate was, however, 66% (four of six) for patients with disseminated CMV, a rate that was significantly higher than the 16% (eight of 49) mortality seen in patients without disseminated CMV infection ($P < .05$). The excess mortality in patients with disseminated CMV may not be attributable solely to CMV, because all these patients had other bacterial or fungal infections that may also have played a role in their deaths.

Transmission. Organ allografts have been shown to transmit CMV to seronegative kidney and heart allograft recipients [11, 15]. The association between receiving a liver from a donor positive for CMV antibodies and subsequent development of CMV infection was analyzed. Thirteen (92%) of 14 seronegative recipients who received livers from CMV-seropositive donors had evidence of CMV infection after transplantation, whereas only one (8%) of 12 seronegative recipients who received a liver from a CMV-seronegative donor developed CMV infection. This difference in infection rate was highly significant ($P < .001$).

No definite relation was found between the occurrence of CMV reactivation infection and the CMV serological status of the donor. Fifteen (71%) of 21 seropositive patients who received a liver from a CMV-seropositive donor underwent CMV reactivation infection; by comparison, 11 (78%) of 14 patients who were seropositive for CMV antibody before transplantation and who received a liver from a CMV-seronegative donor also became infected after transplantation ($P > .5$). This analysis suggests that, as in the case of renal transplant recipients, the organ allograft is not usually responsible for CMV infection in seropositive recipients [11]. All patients received random blood products that were neither tested nor selected for CMV antibody.

The impact of transfusions and blood products on CMV infection in seronegative and seropositive recipients was also investigated. The mean number of units of red blood cells, fresh frozen plasma, cryoprecipitate, platelets, or total units of blood products received by infected and uninfected patients, whether they were seropositive or seronegative before transplantation, was not significantly different. These data are shown in table 2.

CMV infection and immunosuppression. Table 3 shows data on the relation of symptomatic CMV disease and the use of additional immunosuppressive agents such as OKT3, AZA, or steroids. Thirteen (40%) of 32 patients in the OKT3 group developed symptomatic CMV infection; this finding did not differ significantly from the 63% (14 of 22) rate of symptomatic disease in patients who received other immunosuppressive regimens. There was a trend toward more disseminated CMV infections in patients who received OKT3 (six [18%] of 32 vs. 0 [0%] of 23, $P = .06$). Analysis of these data showed that patients with primary infection who received OKT3 had a 55% (five of nine) rate of dissemination as compared with no episodes of disseminated disease in the eight patients with primary infection who did not receive OKT3 ($P = .04$). There was no apparent effect of OKT3 on dissemination in CMV reactivation infection (0 of 15 vs. 1 of 23, $P > .1$).

HSV infection. Of 121 patients, 95 (78%) were seropositive and 26 (22%) were seronegative for antibodies to HSV before transplantation. All but one of the infections caused by HSV occurred in seropositive recipients and were thought to be due to reactivation of latent virus. Of 95 seropositive recipients, 39 (41%) developed typical mucocutane-

Table 3. Relation between additional immunosuppression and symptomatic CMV infection.

Additional immunosuppression	Total no. of assessable patients	No. of patients with				
		Infection	Symptomatic infection	Viral syndrome	Localized CMV infection	Disseminated CMV infection
OKT3*	53	32	13	7	0	6†
AZA only	6	2	2	2	0	0
Steroids only	33	20	12	7	5	0
None	1	1	0	0	0	0
Total	93	55	27	16	5	6

* All patients treated with OKT3 received additional steroids; 17 of 32 infected patients also received AZA (azathioprine).
† $P = .06$ for patients with disseminated CMV disease treated with OKT3 (6 of 32) vs. patients who did not receive OKT3 (0 of 23).

ous HSV lesions, including 29 patients with oral HSV and 10 with genital HSV infections. Two patients developed HSV esophagitis, and two had HSV hepatitis without mucocutaneous lesions. The two cases of hepatitis were discovered at autopsy 21 and 46 d after transplantation. One patient had isolated HSV hepatitis. In the other patient, HSV hepatitis was part of a disseminated visceral HSV infection involving the liver, lungs, colon, and larynx.

Only one of 26 seronegative recipients had primary HSV infection. She developed HSV hepatitis 21 d after transplantation; this finding was documented histopathologically by liver biopsy. HSV was also cultured from a bronchoalveolar lavage specimen. The patient received a liver from a donor seropositive for antibodies to HSV type 2 and developed antibodies to HSV type 2 after transplantation. She was treated with iv acyclovir, and her resolution of HSV hepatitis was documented by falls in transaminase levels and by subsequent liver biopsies.

The oral and genital HSV infections in these patients occurred a median of 19 and 24 d postoperatively, respectively. We did not document HSV viremia or CNS infection from HSV in any patient.

Table 4 analyzes the impact of immunosuppression on HSV infections in seropositive recipients. The group treated with OKT3 had more symptomatic illness due to HSV (29 [53%] of 54), as compared with patients who did not receive OKT3 (13 [31%] of 41, $P = .05$).

EBV infections. Eighty-five of 119 seropositive recipients were assessable for EBV infection, and 20 (24%) of them showed a fourfold or greater rise in antibody titers to EBV VCA. Of these patients, only one patient had symptomatic EBV infection manifested by lymphoproliferative disease 143 d after transplantation. The patient had enlarged periaortic lymph nodes with no evidence of disease outside the abdomen. EBV DNA was found in these nodes by nucleic acid hybridization. He was treated with radiation therapy along with reduction in his immunosuppression, and the disease eventually regressed.

Only two patients in the study population were seronegative for EBV preoperatively. They seroconverted on day 30 and 72, respectively, after transplantation and had no disease attributable to EBV, although one patient had concomitant CMV infection.

Table 4. Immunosuppression in recipients seropositive for HSV and frequency of symptomatic HSV infection.

Additional immunosuppression	Total no. of patients	No. of patients with			Total no. of symptomatic patients
		Oral HSV	Genital HSV	Other HSV infections	
None	1	0	0	0	0
AZA only	5	2	0	0	2
Steroids only	35	7	3	1	11
OKT3*	54	20	7	3	29†
Total	95	29	10	4	42

* All patients treated with OKT3 received additional steroids; 32 of 54 OKT3-treated patients also received AZA (azathioprine).
† $P = .05$ for OKT3-treated patients with symptomatic HSV (29 of 54) vs. symptomatic patients (13 of 41) who did not receive OKT3. One patient had both oral and genital HSV and is counted only once.

Nine (45%) of 20 patients with reactivation EBV infection had symptomatic CMV infection as compared with 17 (26%) of 65 without EBV reactivation. This difference was not statistically significant.

VZV infections. Eight (7%) of the 121 patients developed clinical VZV infection. Seven patients had localized dermatomal zoster that developed a median of 167 d after transplantation (range, 19–575 d). One patient developed fulminant varicella with visceral involvement 32 d after transplantation and died despite treatment with acyclovir.

Discussion

This study is the first to characterize the frequency and morbidity of viral infections in a large group of adult liver transplant recipients and expands upon our previous studies in this population [8]. CMV remains the most important viral pathogen occurring after transplantation. Of 93 assessable patients, 55 (59%) developed CMV infection after transplantation. These results are similar to those reported in renal transplant patients but somewhat lower than those reported in cardiac transplant recipients [16]. An association of symptomatic CMV disease with primary CMV infection has been shown for recipients of kidney and heart allografts [3, 15]. Our results show both an increased incidence of symptomatic CMV infection and a higher frequency of disseminated disease in liver transplant recipients with primary CMV infection. Whelchel et al. [17] have reported a higher mortality rate in renal transplant recipients with symptomatic CMV infection. In our study, the mortality of patients with symptomatic disease (18%) did not differ significantly from the mortality of patients with asymptomatic CMV infection (25%). Disseminated CMV infection was associated with a significantly higher mortality than was nondisseminated CMV infection. However, all four patients with disseminated CMV who died had concomitant systemic bacterial or fungal infections, and their deaths were probably due to multiple factors.

Two important possible sources of CMV acquisition in transplant patients are organ allograft and blood products. Our data show that the hepatic allograft is an important source of CMV infection in seronegative liver recipients. Seronegative recipients who received livers from seropositive donors had an infection rate of 92% (13 of 14). This finding is consistent with similar serological evidence that other major organ transplantation is associated with transmission of CMV [11, 15, 18]. Such evidence has now been further strengthened by proving the identity of donor strains of CMV in renal recipients by endonuclease restriction patterns [19]. In an earlier study we calculated that in the Pittsburgh area, the risk of acquiring CMV infection from transfused units of blood, on the basis of data from seronegative pediatric patients undergoing open heart surgery, was 2.7% per unit [20]. Hence, the risk of CMV infection was low in operations in which usually <10 units were required [21]. However, even in the case of liver transplantation in which significantly more than 10 units of blood and other blood products are used [22], we have not been able to demonstrate an association between primary infection and units of blood used, either in pediatric liver recipients [9] or in adults.

A noteworthy finding in our study is the impact of OKT3 antibodies on CMV infection. OKT3 appeared to increase the risk of dissemination in patients with primary CMV infection. Different immunosuppressive agents may have different effects on CMV infection. Corticosteroids alone appear to have little effect on CMV infection, whereas cytotoxic immunosuppressants such as AZA do have the ability to reactivate latent virus [23]. Since the introduction of CsA into clinical organ transplantation, numerous studies have documented a lower incidence of symptomatic CMV infection in patients treated with CsA [28, 29]. Comparing CMV infection and disease in renal transplant patients receiving either AZA or CsA, but not ATG, we and Bia et al. were unable to show a difference [7, 26]. Rubin et al. [27] have concluded that adding agents such as ATG is more important in potentiating CMV disease than is the basic immunosuppressive regimen. Their conclusions are based on studies that report an increased incidence of symptomatic CMV infection in renal transplant recipients receiving conventional regimens of AZA, prednisone, and ATG, compared with renal transplant patients receiving CsA and prednisone alone [28, 29]. The incidence of symptomatic CMV infection in patients receiving AZA and prednisone without ATG, however, appears to be similar to the rate of symptomatic CMV infection in renal transplant recipients receiving CsA and prednisone [26]. Peterson et al. [30] compared the incidence of CMV pneumonia in a group of renal transplant patients receiving these two regimens and postulated that the higher incidence of CMV pneu-

monia in the group receiving ATG, prednisone, and AZA was related to the use of ATG. Therefore, we believe that the ability to potentiate CMV infections is not unique to OKT3 but that it shares this characteristic with other antilymphocyte preparations. However, because OKT3 was used to treat severe episodes, it may well be that the higher incidence of disseminated CMV infection in these patients was due to a combination of factors such as severe graft rejection along with concomitant bacterial and fungal infections that may have increased their net state of immunosuppression.

As reported in other organ allograft recipients [31], HSV infections were mostly due to reactivation of latent virus. Forty-four percent (42 of 95) of seropositive patients in our study developed symptomatic HSV infection. Of great interest was the case of primary HSV infection (HSV hepatitis) in this study, with a histopathologically documented cure after acyclovir treatment. To our knowledge this is the first reported case of primary HSV hepatitis cured with acyclovir in a transplant recipient. The patient possibly acquired HSV infection from the donor. We have documented probable transmission of HSV infection by the donor organ in kidney recipients, but this route is rare and has not been documented for liver recipients [35, 36].

A few studies have correlated the use of antilymphocyte preparations with an increased risk of reactivation and symptomatic illness due to HSV [32]. Preiksaitis [33] studied heart transplant recipients at Stanford Univeristy (Stanford, Calif) and reported significantly more symptomatic and severe illness due to recurrent herpes labialis in patients treated with high-dose ATG. Similar data are not available for OKT3, but we observed a trend toward a higher frequency of symptomatic HSV infections in seropositive patients treated with OKT3. Most of these infections were mucocutaneous and, therefore, not life-threatening. Because this is a retrospective study, a number of these patients did not have cultures of the lesions performed or were already being treated with acyclovir when cultures were performed. It is our experience in a large transplant population, however, that cultures of typical oral or genital lesions for herpes are almost invariably positive if obtained before antiviral therapy. The number of patients with visceral HSV infections in our study was too small to assess if OKT3 increased the risk of visceral or disseminated HSV. Physicians caring for liver transplant recipients should be aware that visceral HSV infections (particularly hepatitis) may occur in some of their patients. Liver biopsies appear to be diagnostically useful in this setting.

VZV infection was seen in 7% (eight of 121) of our patients. Seven patients had localized zoster. One patient with primary varicella died rapidly of disseminated visceral disease. It is well known that varicella has a high morbidity and mortality rate in transplant recipients [34]. Because hyperimmune globulin against VZV (VZIG) may prevent or ameliorate this illness, it is probably prudent to monitor transplant candidates with no history of chickenpox for VZV antibody to determine their susceptibility to infection. The number of patients with herpes zoster was too small to measure the effect of OKT3 on reactivation.

We found an EBV reactivation infection rate of 24%, which is similar to what was previously reported [12]. In our patients we could not definitely attribute any viral syndrome to EBV, possibly because of simultaneous evidence of CMV infection. One seropositive patient, however, developed an atypical EBV-related lymphoma.

In summary, 65 (53%) of 121 adult liver transplant recipients had one or more symptomatic infections with herpesviruses. Although effective therapy for HSV and VZV infection exists, some cases may still be fatal. CMV infection continues to be a major problem in liver transplant recipients, and active research into the diagnosis, prevention, and therapy of these infections is still needed.

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