

## MINIREVIEW

# Herpesvirus Infections in Organ Transplant Recipients

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Despite great advances in organ transplantation in the last four decades, herpesvirus infections remain a major cause of morbidity and mortality for a majority of transplant recipients. Central to all herpesvirus infections is the virus's ability to establish latent, nonproductive infections which can be reactivated at later times in the host's life, resulting in recurrent infections and associated diseases. While improvements in immunosuppressive drug regimens have decreased the risk of organ rejection, they have not restored the immune competence necessary for the control of primary or reactivated herpesvirus infections. This failure has been offset to a significant degree by the advent of improved techniques for viral diagnosis and monitoring and of new, potent antiviral drugs for prophylaxis and treatment of herpesvirus infections. However, infections caused by the eight human herpesviruses continue to challenge the clinical management of transplant recipients. In this minireview, we focus on recent advances in our understanding of and ability to control herpesvirus infections in organ transplant recipients.

**CMV.** Human cytomegalovirus (CMV; human herpesvirus 5) is a member of the betaherpesvirus subgroup. In developed countries, approximately 40 to 60% of the population has been infected with this virus, and the infection rate increases with age (70). Transmission requires direct contact with infectious virus, which can be shed in the tears, urine, saliva, semen, breast milk, and cervical secretions of infected individuals. The virus can also be transmitted by blood and blood products and by transplantation of infected organs and can be passed vertically from mother to fetus or mother to child (81). In an immunocompetent individual, primary CMV infections are generally asymptomatic, even among infants. In immunosuppressed patients, however, CMV is a major cause of disease and mortality, with a symptomatic infection occurring in 20 to 60% of all transplant recipients (7, 8, 102).

After transplantation, CMV infections can occur as a result of the reactivation of an existing latent infection in the recipient, an infection with a donor strain of CMV, or a primary infection in a previously CMV-naïve individual (usually from the donor organ or blood). In these immunosuppressed individuals, acute CMV infections can lead to a CMV syndrome

characterized by fever, leukopenia, malaise, arthralgia, and/or macular rash (81, 112) or to an invasive disease such as hepatitis or pneumonitis. Chronic CMV infections place the transplant recipient at risk for acute and chronic graft failure as well as secondary immune deficiency and an increased risk of subsequent bacterial or fungal infections (84, 86).

While the precise site for CMV latency is debated, it appears to be within myeloid-lineage hematopoietic cells (70). The mechanisms responsible for CMV reactivation are not clearly understood, but evidence that it may be driven by cytokine production in the host following immune activation has been accumulating. Viral reactivation is most likely regulated at the transcriptional level by the major regulatory proteins, IE-1 and IE-2 (70). Several laboratories have reported that proinflammatory cytokines such as tumor necrosis factor alpha, interleukin-1 $\beta$  (IL-1 $\beta$ ), and IL-4 are capable of stimulating gene expression from these immediate early promoters in transient-expression assays as well as viral replication in cell cultures (26, 91, 106). Evidence linking the reactivation of CMV to tumor necrosis factor alpha not only among transplant recipients but also in patients with sepsis, end-stage liver cirrhosis, or severe psoriasis has been reported (5, 19, 53).

To add further insult to the host, the CMV genome encodes several proteins capable of helping virus-infected cells evade the immune system. These proteins downregulate major histocompatibility complex class I molecules, block transporter molecules involved in antigen processing, and upregulate the major histocompatibility complex class I HLA-E molecule, which can inhibit NK cell-mediated lysis (91). CMV also encodes an IL-10 homologue that can block proinflammatory cytokines and suppress macrophage functions associated with antigen presentation (91). Regardless of these immunomodulatory effects, CMV infection in transplant recipients has been treated by infusion of anti-CMV cytotoxic-T-lymphocyte (CTL) clones derived from ex vivo culture (90).

For detection of CMV infection, analysis of serum for CMV antibodies is useful for determining prior CMV infection but much less so for determining viral reactivation or new infection, as the patient's ability to mount normal humoral immune responses may be blunted. Assays to detect infectious virus include conventional cell culture (which can require several weeks of incubation) and a faster shell vial assay (which provides results within 48 h). Both assays are subject to the potential problems arising from the fact that the proper collection, shipment, and storage of samples are critical for maintaining virus viability. In addition, asymptomatic shedding

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of virus in the respiratory, urinary, or gastrointestinal tract can occur without clinical consequence. Acute viral infections can also be detected by analysis of blood samples for the presence of CMV antigens (the antigenemia assay). These results can be obtained within 1 day, but the assay also involves special collection, shipment, and storage requirements. Finally, active CMV infections can be determined by the detection of CMV DNA in peripheral blood samples by using qualitative or quantitative PCR techniques. Quantitative PCR is useful in monitoring ongoing CMV-related disease as well as in predicting CMV disease (83). PCR results can be obtained within 24 h, and the assay does not have the special requirements for collection, handling, and storage that the antigen and infectious virus assays do. Detection of CMV RNA in blood, which has also been reported to have a high correlation with CMV disease, is a method used by some diagnostic laboratories, as a Food and Drug Administration-approved test is available commercially.

Before the availability of herpetic antiviral drugs, treatment of a transplant recipient for CMV-related disease consisted of a reduction in the immunosuppressive regimen, which often led to an increased incidence of graft rejection (102). With the development of specific antiviral agents, it is now often possible to maintain the level of immunosuppression required to prevent graft rejection. The drug of choice against CMV is intravenous ganciclovir. Under conditions of ganciclovir resistance or a failure of ganciclovir treatment, foscarnet or cidofovir is often used. Foscarnet is also given intravenously but has several serious side effects, including nephrotoxicity, nausea, vomiting, anemia, and seizures (52). Cidofovir, a nucleotide analog of cytosine, is not herpes specific and has activity against several other viruses, including adenovirus, hepatitis B virus, and human papillomavirus (102). Its use is limited by significant nephrotoxicity.

Valganciclovir and valacyclovir are newer drugs currently under investigation for treatment of CMV disease in transplant recipients. Both drugs can be administered orally and have increased oral bioavailability compared to that of acyclovir or ganciclovir (60). The effective use of oral antiviral agents for both prevention (valacyclovir and ganciclovir) and treatment (valganciclovir) of CMV disease would represent a significant improvement in CMV disease therapy among transplant recipients. However, the ease of administration of these drugs also leads to a substantial risk of inappropriate overuse and increased viral resistance.

**EBV.** Epstein-Barr virus (EBV; human herpesvirus 4) is a gammaherpesvirus that is the cause of infectious mononucleosis, Burkitt's lymphoma, nasopharyngeal carcinoma, and post-transplant lymphoproliferative disease (PTLD). The virus is excreted in saliva and spread by close contact, often infecting hosts of a young age. Primary infection is usually asymptomatic but can manifest as mononucleosis in young adults. Infection in the immunocompromised host is accompanied by the risk of developing lymphoproliferative diseases. Over 90% of adults are seropositive for EBV infection and thus harbor latent virus that is periodically reactivated.

By far, the greatest risk for serious EBV disease in transplant recipients is PTLT. Estimates of PTLT frequency have ranged from 0.5 to 23% in organ allograft recipients (3, 17, 23, 46, 75, 89). In general, seronegative recipients of an organ from

a seropositive donor are at highest risk for the development of PTLT. However, all intestinal transplant recipients are at risk, regardless of serologic status for EBV.

At the time of PTLT diagnosis, there is almost always a large circulating load of EBV in the peripheral blood (51, 93). The viral load exceeds by several orders of magnitude the amount of virus detected in the typical latent state in a healthy carrier. Because of this increased viral load, quantitative PCR methods for detection of EBV are a useful adjunct for the diagnosis of PTLT. Indeed, because the viral load in the peripheral blood appears to rise in advance of other clinical signs of lymphoproliferative disease, prospective monitoring for viral load has been used to predict lymphoproliferative disease. Reduction of peripheral viral load with resolution of the PTLT is also a sign used to monitor the progress of therapeutic interventions (94).

Development of EBV-driven PTLT may be viewed as a direct consequence of the immune suppression necessary to prevent rejection in solid-organ transplant recipients. In 1984, Starzl et al. first suggested that reduction or withdrawal of immune suppression was a frontline strategy for the treatment of PTLT (107). Subsequent studies confirm that this is an effective initial strategy for the treatment of most categories of EBV disease (14, 46, 111). The goal of this approach is to allow host immune surveillance to control the proliferation of EBV-infected cells. In 1982, Hanto et al. described a patient whose EBV-associated PTLT lesion appeared to respond to acyclovir treatment (36). Since then, the use of acyclovir or ganciclovir for the treatment of EBV-driven PTLT has become common (6, 9, 35, 76). However, the efficacies of these drugs have not been established in prospective, comparative clinical trials (46). Evidence against a major therapeutic role for these agents in the treatment of EBV-driven PTLT in solid-organ transplant recipients comes from the observations that EBV loads in the peripheral blood have risen and that PTLT developed while patients were receiving intravenous acyclovir (31, 64) or ganciclovir (6, 31, 57).

Intravenous immunoglobulin (IVIG) for the treatment of EBV-driven PTLT has also been used in combination with other treatment modalities (42, 50, 101, 109). While a number of transplant centers incorporate IVIG in their standard prophylactic regimens, well-designed clinical trials evaluating the potential role of IVIG in the prevention of PTLT have not been reported (32).

Some early case reports on the use of anti-B-cell antibodies for the treatment of lymphoproliferative disorders have suggested that this approach may have therapeutic value in the control of EBV-driven PTLT (27, 55). Rituximab (a humanized murine monoclonal antibody that recognizes the CD20 antigen on B cells) is the next-generation immunoreagent that circumvents some of the problems associated with mouse antibody therapy. It has recently been approved for the treatment of certain CD20-positive-B-cell non-Hodgkins lymphomas (66), and anecdotal studies have reported favorable responses in PTLT patients, although relapses do occur (22, 24, 34, 114, 120, 122).

CTLs directed against EBV antigens are the main immune mechanism controlling EBV infection in immunocompetent individuals (92). Thus, EBV-specific CTLs have been developed and applied as therapy for the management of PTLT.

Protocols for the generation of autologous anti-EBV T cells for adoptive therapy in both bone marrow and solid-organ transplant recipients have been reported (47, 48, 80, 92, 98), with at least one report showing complete remission of lymphoproliferative disease in a liver-small bowel transplant recipient (37). This success suggests that in the near future an HLA-defined CTL bank could supply cells for antiviral immunotherapy for immunocompromised patients.

**HSV.** Herpes simplex virus type 1 (HSV-1; human herpesvirus 1), an alphaherpesvirus, often infects individuals early in life, leading to a seroprevalence of 50 to 80% among adults in Western countries. The seroprevalence of sexually transmitted HSV-2 (human herpesvirus 2) in adults has increased in the last few decades to levels of 15 to 50% depending on age, gender, and race. Both viruses establish a latent infection in the trigeminal ganglion (HSV-1) or sacral ganglion (HSV-2), with reactivation being common. Donor transmission is rare, as the site of latency is not transplanted.

Prior to the onset of antihherpetic drug prophylaxis, recurrent HSV-1 or HSV-2 infections accounted for as much as 70 to 80% of severe mucocutaneous diseases in allogeneic bone marrow or blood progenitor cell transplant recipients and affected a significant but lesser number of solid-organ transplant recipients (68, 69). Typically, reactivated localized HSV infections occur within the first few weeks of transplantation, while the more serious HSV systemic disease or encephalitis occurs rarely in transplant recipients (95).

The widespread application of intravenous and oral acyclovir prophylaxis in the early 1980s, together with therapeutic regimens involving these drugs, largely erased the specter of HSV-related disease for transplant patients (30, 59, 69, 82, 97, 100). However, HSV infections continue to result in significant disease in some progenitor cell transplant recipients (10), even in those with HLA-haploidentical donors (54). HSV infection transmitted by means of transplanted corneas to HSV-seronegative recipients can result in serious HSV disease (87). These infections are increasingly caused by antiviral-drug-resistant HSV mutants that evolve under pressure of prophylactic as well as therapeutic drug regimens (10, 13, 54, 113).

Diagnosis of HSV infection is still achieved predominantly by culture of infectious virus from lesion fluids or mucosae, supplemented by direct staining of cells from these specimens or viral isolates with fluorescent-dye-conjugated monoclonal antibodies specific for HSV-1 and HSV-2 antigens (58). Molecularly based techniques such as PCR are critical for diagnosis of HSV encephalitis and are also useful for detecting corneal infections, but they are not routinely used for the detection of mucocutaneous HSV infections.

**VZV.** Varicella-zoster virus (VZV; human herpesvirus 3) is an alphaherpesvirus whose primary infection usually manifests as chicken pox (varicella). After the initial infection of mucosal or skin cells, the virus infects CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocytes that circulate via the blood to disseminate virus in cutaneous and visceral regions. Over 90% of adults have had VZV by their 20s and thus harbor latent infection in their dorsal root ganglia. Reactivation results in the development of herpes zoster (shingles).

Young pediatric transplant recipients without preexisting immunity to VZV are at risk for developing primary VZV infections after exposure to chicken pox. Prior to the availabil-

ity of acyclovir, these patients were at risk for significant morbidity and mortality (4, 25, 65).

One approach for prevention of primary and reactivated VZV infections in transplant recipients is vaccination with a live, attenuated VZV vaccine. Active vaccination with the live, attenuated VZV vaccine prior to renal transplantation may be beneficial in children at risk for primary VZV infection (77), but this vaccine has had little effect on the incidence or severity of varicella infection after liver transplantation (21). Moreover, the live vaccine strain can undergo latency and reactivate after transplantation. An inactivated VZV vaccine currently in clinical trials may be safer than the attenuated vaccine yet retain potent T-cell-stimulatory properties (4).

VZV infections are routinely diagnosed by clinical presentation. To confirm the diagnosis, virus can be identified by culture or by immunofluorescent staining with monoclonal antibody (108). Culture assays require from several days to weeks to complete, whereas an immunofluorescent-antibody assay (IFA) can be completed within a few hours.

The standard treatment of VZV infections in transplant recipients is high-dose intravenous acyclovir (4, 73, 88). Alternative treatments include high-dose oral acyclovir and other nucleoside analogs, such as valacyclovir and famciclovir. Passive immunization with VZV hyperimmune globulin within 72 h of exposure is the only established preventive approach for transplant recipients.

**HHV-6 and HHV-7.** Human herpesvirus 6 (HHV-6) and HHV-7 are members of the betaherpesvirus subgroup. HHV-6 was discovered and first isolated in 1986 (96) from circulating lymphocytes of patients with lymphoproliferative disease. HHV-6 isolates have been classified into two variant classes, HHV-6A and HHV-6B, which are closely related genetically but have different biological, molecular, and epidemiological properties. HHV-6B is the primary causative agent of exanthem subitum (119), while HHV-6A has not been clearly associated with any known disease or syndrome.

HHV-7 was discovered in 1990 (29) from the blood cells of a healthy individual. HHV-7, like HHV-6A, does not have a clear association with any known disease, although it has been reported to be responsible for some cases of exanthem subitum (110).

Both HHV-6 and HHV-7 replicate primarily in T cells, although HHV-6 can also infect B cells, NK cells, and monocytes (118). Both viruses are ubiquitous, with primary infections occurring very early in childhood (117), and thus the majority of older children and adults (>90%) are dually seropositive. While the exact route of transmission is under debate (118), horizontal spread by virus shed in saliva appears to be the most logical route for both viruses.

Both HHV-6 and HHV-7 establish latent infections, possibly in monocytes (118). The frequency of reactivation among immunocompetent individuals is not known, and there is no disease associated with reactivation among healthy individuals. There is however, clear evidence for reactivation among immunosuppressed individuals, such as AIDS patients and transplant recipients. Indeed, HHV-6 infection or reactivation occurs in 38 to 60% of bone marrow transplant recipients and in 31 to 55% of solid-organ transplant recipients (103). Reactivation of HHV-6 generally occurs during the first month following transplantation, and the reactivated virus is almost ex-

clusively variant B. Similarly, HHV-7 has also been found to reactivate following transplantation (67, 78, 79).

Both HHV-6 and HHV-7 have been associated with allograft rejection, marrow suppression, and an increased risk for development of CMV disease (33, 85, 104). There is also evidence for direct interactions between HHV-6 and HHV-7 as well as immune response involvement in viral reactivation (45, 67, 79). Moreover, HHV-6 reactivation is associated with CMV disease among allogeneic bone marrow and solid-organ recipients (18, 20, 41, 44). These reports suggest that reactivation of HHV-6 and/or HHV-7 in combination with CMV results in a significantly increased risk of symptomatic disease compared with that from either of the viruses alone.

Serological assays are not useful in monitoring transplant patients for viral reactivations since most individuals seroconvert at very early ages. Although both HHV-6 and HHV-7 can be found in circulating lymphocytes and saliva, detection of virus in saliva is not useful since shedding occurs in asymptomatic individuals (38, 40, 49, 56). As a result, viral monitoring of HHV-6 or HHV-7 should be performed on circulating lymphocytes. The detection of either virus can be accomplished by direct isolation of infectious virus or by detection of viral DNA by PCR.

While there have been several reports on the effects of different antiherpetic compounds on HHV-6 and HHV-7 replication in vitro (2, 39), there are very few reports on the use of these compounds in vivo (15, 67).

**HHV-8.** HHV-8, or Kaposi's sarcoma (KS)-associated herpesvirus, a gammaherpesvirus, is the most recently discovered lymphotropic human herpesvirus (11). It is the causal agent of KS, a unique body-cavity-based lymphoma, and some forms of multicentric Castlemann's disease (12, 99, 116).

The iatrogenic form of KS is seen in solid-organ transplant recipients with a prevalence of 0.5 to 5%, depending on the patient's country of origin, and occurs 1,000-fold more often in transplant recipients than in age-matched controls (63). The occurrence of KS among transplant recipients is associated with the immunosuppressive therapy (particularly calcineurin inhibitors), as evidenced by the remission of KS lesions following the reduction or withdrawal of the immunosuppressive therapy (1, 71, 72, 74).

Several case control studies note the development of KS to be associated with the reactivation of HHV-8 in the transplant recipient (28, 61). In a recent study, HHV-8 was shown to reactivate among transplant recipients who were seropositive prior to transplant and a significant number of seronegative patients, including children, were shown to seroconvert to HHV-8 following the transplant (43). The route of transmission of HHV-8 among these seroconverters is unknown, but at least three separate routes (donor organ, blood transfusions, caregivers) have been proposed.

Among healthy adults, primary HHV-8 infection appears to be fairly mild, with no obvious signs of clinical disease (115). The most commonly reported clinical manifestation of HHV-8 infection in transplant recipients is KS. The KS prevalence rate of 0.5% among solid-organ transplant recipients in the United States is much lower than the 20% HHV-8 seroprevalence rate reported for this same group (43). The discrepancy between the frequency of KS and the HHV-8 seroprevalence in transplant recipients suggests that the majority of HHV-8 reactiva-

tions or primary infections in this population do not result in clinical disease. However, Luppi and coworkers (62) have reported an acute virus-like syndrome (fever, splenomegaly, and cytopenia) in an HHV-8-seronegative kidney transplant recipient who received a kidney from an HHV-8-seropositive donor. The patient suffered bone marrow failure and ultimately died of renal and cardiac failure. They also reported an HHV-8 reactivation event in an autologous stem cell transplant patient that coincided with the appearance of fever and bone marrow aplasia with plasmacytosis.

HHV-8 is not ubiquitous in the general healthy population (it has a seroprevalence of 2 to 10%), and therefore serology is more useful than other methods in detecting primary infections. Current serological assays are IFAs using HHV-8-infected B-cell lines and enzyme-linked immunosorbent assays that use isolated HHV-8 proteins or manufactured viral peptides. Both types of assays can detect antibodies directed against viral proteins expressed during a lytic, replicative cycle or during latency. While there is some debate regarding which assay is most accurate, the IFA using lytic cycle antigens appears to be the most sensitive assay, with good specificity (16, 105, 121). Serology is also the most accurate method for determining prior HHV-8 infection since viral DNA is not commonly found in circulating lymphocytes of seropositive individuals (105).

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