Cytomegalovirus and Other β-Herpesviruses

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Summary: Cytomegalovirus (CMV), human herpes virus (HHV)-6, and HHV-7 are ubiquitous β-herpesviruses that can cause opportunistic infection and disease in kidney transplant recipients. Active CMV infection and disease are associated with acute allograft failure and death, and HHV-6 and HHV-7 replication are associated with CMV disease. CMV prevention strategies are used commonly after kidney transplantation, and include prophylaxis with antiviral medications and preemptive treatment upon the detection of asymptomatic viral replication in blood. Both approaches decrease CMV disease and allograft rejection, but CMV prophylaxis is preferred for high-risk patients because it is easy to administer and may be more effective in real-world settings. CMV disease commonly occurs even with current preventive strategies, whereas HHV-6 and HHV-7 diseases are rare. The clinical manifestations of CMV, HHV-6, and HHV-7 are nonspecific, and laboratory confirmation is essential to establishing diagnoses. Although nucleic acid testing has supplanted other diagnostic modalities given its high sensitivity and specificity, histopathologic examination sometimes is necessary to identify disease definitively. Ganciclovir and valganciclovir are the treatments of choice for CMV and HHV-6, and foscarnet can be used to treat HHV-7. Treatment duration should be informed by the initial severity of disease, and subsequent clinical and virologic responses.
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Cytomegalovirus (CMV), human herpes virus (HHV)-6, and HHV-7 are globally widespread viruses that are characterized by encapsidated linear double-stranded DNA genomes, temporally ordered gene expression, broad tissue tropism, latency after primary infection, periodic reactivation, and direct person-to-person transmission.[1] These viruses are classified as members of the *Herpesvirales* order, *Herpesviridae* family, and *Betaherpesvirinae* subfamily; HHV-6 and HHV-7 are members of the *Roseolovirus* genus; and HHV-6 is divided into two genetically and phenotypically distinct variants referred to as HHV-6A and HHV-6B.[1–4]

A CMV virion is composed of an icosahedral nucleocapsid surrounded by tegument and a lipid envelope with glycoproteins enclosing a large linear double-stranded DNA genome[5-7] (Fig. 1). Replication is characterized by the sequential expression of immediate-early genes, which primarily are transcriptional regulators, early genes that are involved in DNA replication, and late genes that encode viral structural and assembly proteins.[2,8–10] Tropism for human cells is broad, and varies by virus. CMV replicates in various leukocyte populations, connective tissue cells, hepatocytes, epithelial cells, and endothelial cells.[11] HHV-6 replicates in T lymphocytes, connective tissue cells, hepatocytes, epithelial cells, and endothelial cells.[12] HHV-7 replicates in T lymphocytes, macrophages, and hematopoietic precursor cells.[13] CMV, HHV-6, and HHV-7 persist indefinitely in the host, which derive from the ability of their genomes to be maintained in covalently closed circular episomes within cell nuclei.[14–16] In addition, the HHV-6 genome can be integrated within the subtelomeric region of human chromosomes,[17,18] a unique feature that allows person-to-offspring transmission through germinal cells.[19] Reactivation occurs through transcription of immediate-early genes after transactivation by cellular and/or viral factors, and results in low-level productive infection in some cells and fully lytic infection in others.[20–22] In solid-organ transplant recipients, triggers for reactivation include increased immunosuppression, acute allograft rejection, inflammation, and concurrent other infection.[23] CMV, HHV-6, and HHV-7 are shed in saliva, urine, and other bodily secretions, and interhost transmission occurs primarily through direct person contact.[2,24] Blood transfusion and contact with environmental surfaces containing live virus also can result in transmission.[25,26] In solid-organ transplant recipients, primary infection can occur through receipt of an organ from a donor with latent viral infection.[27–29]

EPIDEMIOLOGY

General Epidemiology

CMV, HHV-6, and HHV-7 are ubiquitous viruses that are found in human populations worldwide, and typically are acquired early in life. Seroepidemiologic studies of persons from developed countries have shown prevalences of 51%, 90%, and 95% for CMV, HHV-6, and HHV-7, respectively.[12,30,31] Current

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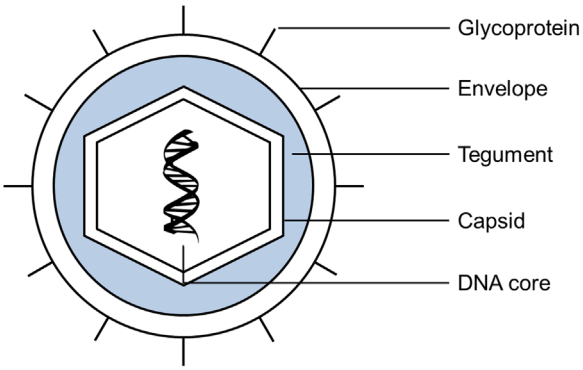

Figure 1. Diagram of β-herpesvirus structure.

serologic techniques cannot differentiate between HHV-6A and HHV-6B. Seroprevalence rates vary depending on age (higher in older persons), socioeconomic status (higher in economically disadvantaged persons), and geography (higher in developing countries).

CMV in Kidney Transplant Recipients

The epidemiology of CMV infection among kidney transplant recipients is well defined. Among US kidney transplant recipients, 18% are seronegative recipients of kidneys from seropositive donors (D+/R−), 61% are seropositive patients (R+) and 21% are D−/R−.[32,33] Kidney transplant recipients receive immunosuppressive regimens to prevent acute allograft rejection,[34] which increases their risk of active CMV infection (defined as detectable CMV replication in blood), or CMV disease (defined as detection of CMV in a clinical specimen accompanied by CMV syndrome or tissue-invasive CMV disease).[35] Before the era of effective CMV prevention, active CMV infection occurred in 69% and 67% of D+/R− and R+ patients, respectively, and CMV disease occurred in 56% and 20% of D+/R− and R+ patients, respectively, within 3 months of transplant.[36] Natural history studies have shown that active CMV infection and disease are associated with a 1.6- and 2.5-fold increased risk of acute allograft rejection, and a 2.8- and 2.5-fold increased risk of death, respectively.[37,38]

Widespread adoption of CMV prevention strategies by transplant centers has changed the epidemiology of CMV infection after kidney transplantation. Different CMV prevention strategies include prophylaxis with antiviral medications, and preemptive treatment upon the detection of asymptomatic viral replication in blood.[39] In a single-center study of 176 D+/R− patients who received prophylactic ganciclovir or valganciclovir for 3 months, 29% of patients developed CMV disease at a median of 61 days after stopping antiviral prophylaxis, of which 49% were CMV syndrome and 51% were tissue-invasive CMV disease. The investigators reported that tissue-invasive CMV disease was associated with a 2.8-fold increased risk of allograft loss or death, whereas CMV syndrome was not.[27] In a multicenter study of 15,848 US kidney transplant recipients assembled using large administrative data, CMV disease occurring more than 100 days post-transplant was identified in 4.0% of patients, and CMV disease occurring 100 days or fewer post-transplant was identified in 1.2% of patients. In multivariable analysis, CMV disease occurring 101 to 365 days post-transplant and CMV disease occurring more than 365 days post-transplant was associated with a 1.5- and 2.1-fold increased risk of death, respectively.[40] Taken together, these studies show that although the incidence of CMV disease after kidney transplant has decreased in the era of preventive strategies, CMV continues to affect transplant outcomes adversely, and better and more enduring preventive strategies are needed, especially for D+/R− patients.

HHV-6 and HHV-7 in Kidney Transplant Recipients

The epidemiology of HHV-6 and HHV-7 infection in kidney transplant recipients is less well -defined. Given that the seroepidemiologic prevalence of HHV-6 and HHV-7 in the general population is approximately 90% to 95%,[12,31] it is assumed that the majority of kidney transplant recipients are latently infected at the time of transplant, and that most cases of viral replication relate to reactivation as a result of immunosuppressive therapy. Without the administration of ganciclovir or valganciclovir for CMV prophylaxis, the incidence of active HHV-6 and HHV-7 infection defined as new-onset IgM seropositivity was reported to be 31% and 52%, respectively.[41,42] With the administration of ganciclovir or valganciclovir for CMV prophylaxis, the incidence of active HHV-6 and HHV-7 infection defined as the detection of viral replication in blood using polymerase chain reaction (PCR) has been reported to be 20% and 75%, respectively.[43] Although different laboratory methodologies were used to detect active viral infection between historical and more contemporary studies (nucleic acid testing likely confers greater sensitivity for detecting active infection), these results suggest that ganciclovir and valganciclovir can suppress HHV-6 replication but not HHV-7 replication, and are supported by in vitro susceptibility studies that show that the half-maximal response values of ganciclovir were 0.65 μg/mL for HHV-6A, 1.33 μg/mL for HHV-6B, and greater than 7 μg/mL for HHV-7.[44] Both HHV-6 and HHV-7 have been linked to an increased risk of CMV disease and acute allograft rejection in studies wherein no CMV prophylaxis was given.[29] More contemporary studies wherein CMV prophylaxis was administered showed no increased risk of CMV disease or acute allograft rejection with HHV-6 or HHV-7 viral replication,