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# A review of Herpesvirus Infections in Kidney Transplant Recipients: Diagnosis, Treatment, and Preventive Strategies

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## ABSTRACT

Today, kidney transplantation is one of the best treatment methods for people with chronic kidney failure, and a large number of kidney transplants are performed worldwide every year. Pathogens that commonly infect kidney transplant recipients are viruses, bacteria, and protozoa. Among these, viruses are considered one of the biggest life-threatening factors in kidney transplant recipients. The reactivation of herpes viruses from the latent state often occurs in conditions of weakening the immune system, including after kidney transplantation, Infection with herpes viruses is still one of the main causes of complications and death for most kidney transplant recipients. Rapid diagnosis of active infection of these viruses in kidney transplant patients has a significant impact on the use of appropriate treatment strategies to reduce complications and transplant rejection. For this reason, this review aims to provide information about the clinical spectrum, diagnosis, and treatment of herpes virus infections in kidney transplant recipients.

**Keywords:** Human herpesviruses, kidney transplantation, kidney transplant recipients.



## INTRODUCTION

Despite the significant progress made in the field of organ transplantation over the last four decades, infection with herpes viruses continues to pose a substantial threat to the majority of transplant recipients (1). Organ transplant recipients require immunosuppressive drugs to preserve the transplanted organ, but this reduces their defense mechanisms, especially the function of T lymphocytes and the production of IFN-γ and tumor necrosis factor-α (TNF-α) against pathogens (2, 3). In addition to the direct and indirect effects of viral infection, some viruses can significantly increase the risk of malignancy in transplant recipients (2). The emergence of enhanced methods for the identification and surveillance of viral pathogens, coupled with the development of novel antiviral medications for the prophylaxis and management of herpes infections, has partially mitigated this issue. However, infections caused by human herpesviruses continue to challenge the clinical management of transplant recipients. *Herpesviridae* family is a large group of DNA viruses that are classified into three subfamilies named alpha, beta, and gamma *herpesvirinae*. Alpha herpes virinae includes herpes simplex virus type 1 (HSV-1), herpes simplex type 2 (HSV-2), and varicella-zoster virus (VZV). Beta herpesvirinae includes cytomegalovirus (CMV),

human herpesvirus 6 (HHV-6), and human herpesvirus 7 (HHV-7). Gamma herpesvirinae includes Epstein-Barr virus (EBV) and human herpesvirus 8 (HHV-8) (4). All herpes viruses remain dormant after entering the host's body and cause a persistent infection. Given that the reactivation of herpes viruses from the latent state often occurs in the setting of immunocompromised states, such as post-organ transplantation, this review aims to provide updated insights on the clinical spectrum, diagnosis, and management of herpes virus infections in kidney transplant recipients (1). In the following, we explain each of these viruses.

**Herpes simplex virus type 1 and 2:**

Herpes simplex virus type 1 (HSV-1) typically infects individuals during childhood, leading to a seroprevalence of 50–80% among adults in Western countries. The seroprevalence of sexually transmitted herpes simplex type 2 (HSV-2) in adults has risen by 15% to 50% in recent decades, varying based on age, gender, and ethnicity (1). The incidence of HSV infection among individuals who have undergone solid organ transplantation has been reported as 29 cases per 1000 person-years (5). Both viruses are responsible for inducing a latent infection in either trigeminal ganglion (HSV-1) or sacral ganglion (HSV-2) (1). HSV-1 and HSV-2 frequently reactivate in immunocompromised conditions following kidney transplantation. Among kidney transplant recipients, skin, mucosal, oral, or genital diseases are the most common clinical manifestation of HSV-1 and HSV-2 infections (6) and the resulting lesions are typical, vesicular or ulcerative while more serious systemic disease or encephalitis rarely occurs in these individuals (1).

Diagnosis of HSV infection is primarily accomplished through the cultivation of the infectious virus from lesion fluids or mucus and staining cells from these samples with fluorescent monoclonal antibodies. Molecular techniques such as polymerase chain reaction (PCR) are indispensable for the diagnosis of HSV encephalitis but are not commonly employed in the diagnosis of mucosal HSV infections (1). In transplant recipients, it is generally agreed that mild, localized, limited disease should be treated with oral antiviral therapy while severe, disseminated, or invasive disease should be treated with intravenous therapy. Limited mucocutaneous HSV disease can be treated with oral acyclovir, valacyclovir, or famciclovir. The treatment duration is 7 to 10 days, although it is plausible to extend the treatment until the complete healing of all lesions is achieved. Disseminated, visceral or extensive HSV disease should be treated with intravenous acyclovir at a dose of 5 to 10 mg/kg every 8 hours (6). The widespread use of prophylaxis and regimens of intravenous and oral acyclovir in the early 1980s greatly reduced the spectrum of HSV-related disease in renal transplant recipients (1).

**Varicella zoster virus (VZV):**

Over 95% of adults are seropositive for VZV and have latent infection in their dorsal root ganglion. The incidence rate is 55 cases per 1000 people per year in lung transplants, 32 cases in heart transplants, 20 cases in kidney transplants (5), and among patients with end-stage renal disease (ERSD) with a hazard ratio of 1.4 to 3.6 compared to the general population (7).

Similar to the general population, kidney transplant recipients can experience two types of clinical disease from VZV infection: The first is the primary infection leading to chickenpox with widespread vesicular lesions on the trunk, head, and limbs. The second is herpes zoster (HZ), arising from virus reactivation and is characterized by the development of a painful blister on one side of the skin (1, 6). After the initial infection of mucosal or skin cells, the virus infects T CD4+ and T CD8+ lymphocytes, leading to virus replication in the skin and visceral regions. Kidney transplant recipients without pre-existing immunity to varicella-zoster virus (VZV) are at risk of developing chickenpox (1). Administering the live attenuated VZV vaccine to these individuals before kidney transplantation can be advantageous. Individuals who remain VZV seronegative are eligible for post-exposure prophylaxis with VZV immunoglobulin (VariZIG) within the first 10 days after exposure (5). Post-herpetic neuralgia (PHN) develops in 20-40% of kidney transplant recipients (8). This is probably due to the disruptive effects of uremic toxins on the immune system, malnutrition,

chronic inflammation, and premature thymic atrophy, which lead to reduced T-cell percentages and reduced T-cell receptor diversity in ESRD patients (7). The recommendation is to give either the live attenuated HZ vaccine (Zostavax®, Merck & Co., Inc., USA) or its recombinant subunit vaccine to individuals over the age of 60 before undergoing kidney transplantation (5, 8). The live attenuated HZ vaccine is approximately 70% effective in preventing HZ in people aged 50 to 59 years, but its effectiveness declines with age and is not recommended for use in immunosuppressed individuals. In contrast, the recombinant HZ subunit vaccine provided more than 95% protection for healthy people in the same age range and is safe for use in immunocompromised people (5). Prophylactic administration of this vaccine before transplantation can reduce the incidence of herpes zoster and its severity after transplantation (7).

VZV infections are typically diagnosed by clinical manifestations. Confirming the diagnosis may require detecting the virus through culture or immunofluorescence staining using a monoclonal antibody. Virus culture requires a longer time, ranging from several days to weeks, whereas immunofluorescence antibody assays (IFA) can yield results within hours (1).

Mild localized cutaneous herpes zoster is typically managed with the administration of oral valacyclovir given at elevated dosages. In kidney transplant recipients, skin disease in sensitive regions such as the face is initially treated through the use of intravenous antiviral drugs (similar to those employed for primary varicella or disseminated disease). This precaution is necessary due to the potential involvement of the eye or facial nerve. The treatment duration generally spans from 7 to 10 days, and occasionally the drug is prescribed for longer periods until the skin lesions have reached a dry (crusted) state (6). The recommended treatment for disseminated VZV infection in kidney transplant recipients is the administration of a high-dose intravenous acyclovir. Alternative treatments such as high-dose oral acyclovir or other nucleoside analogs like valacyclovir and famciclovir may be employed (1). If there is sensitivity or resistance to these medications, foscarnet and cidofovir are replaced (5). Passive immunization with VZV immunoglobulin within the first 72 hours after exposure to infection is the only prophylactic measure for kidney transplant recipients (1).

**Cytomegalovirus (CMV):**

In developed countries, approximately 40 to 60 percent of the population has been infected with this virus in childhood, and the rate of infection increases with age. The virus can be transmitted through contact with tears, urine, saliva, semen, breast milk, and cervical secretions of infected people, blood, transplant of infected organs, and vertically from mother to fetus. In immunocompetent individuals, primary CMV infections are generally asymptomatic. However, in immunosuppressed patients, CMV poses a significant risk of morbidity and mortality making it the most common virus to infect kidney transplant recipients (9, 10). Before the use of prophylactic drugs, the prevalence of the virus was present in 50% of kidney, liver, and heart transplant recipients and 70% of lung transplant recipients. Nowadays, with the development of antiviral drugs and the availability of high-sensitivity tests for rapid detection of the virus, the occurrence of HCMV infection in patients has decreased. Nevertheless, it remains a prevalent infection post-transplantation, reaching 20% in some high-risk patients (11). Transplant recipients can experience three types of CMV infection primary infection (seen in D+/R- recipients), secondary or reactivated infection (in HCMV-positive recipients, the latent virus can reactivate) and superinfection (A different virus is transmitted from the transplanted organ to the recipient who did not have it previously) (12). Typical CMV disease presents with fever, anorexia, myalgia and headache. These symptoms usually occur between 1 and 4 months after transplant. However, the onset of CMV disease may occur later if the patient receives prophylactic treatment with intravenous ganciclovir or valganciclovir. This disease is often associated with anemia, leukopenia, thrombocytopenia, mild lymphocytosis with atypical lymphocytes, and mild hepatitis. Some patients, especially those affected by primary infection, may develop pneumonia, gastrointestinal complications, encephalitis, or

myocarditis. Also, CMV may lead to acute graft rejection and in the long term cause interstitial tubular fibrosis and chronic allograft rejection (9, 13). Several proteins encoded in the CMV genome can suppress MHC-I molecules and prevent NK cell-mediated lysis. These proteins also inhibit pro-inflammatory cytokines by producing an IL-10 homolog and reduce the function of host macrophages. This ultimately allows the virus to evade the host's immune system (1, 14). Risk factors for CMV infection include low lymphocyte count, low complement or NK cells, IgG hypo gammaglobulinemia, donor and recipient CMV serology mismatch, and use of lymphocyte-depleting drugs, donor and recipient age, transplant type, race, and underlying diseases (2, 15).

Antibody serology tests that measure the avidity maturation of HCMV-specific IgG antibodies can be used to determine if someone has past or current HCMV infection (16). Cell culture is one method of detecting infectious viruses, but it can take several weeks. Shell vial which provides results within 48 hours is a faster assay. Acute viral infections can be diagnosed by testing for CMV antigen in the blood. Active CMV infection can be determined by detecting CMV DNA in peripheral blood samples using quantitative or qualitative PCR techniques (1, 17).

The drug of choice is intravenous ganciclovir. If ganciclovir is not successful, foscarnet or cidofovir may be considered as alternatives. Foscarnet, which is also given intravenously, can cause serious side effects, including nephrotoxicity, nausea, vomiting, anemia, and seizures. The use of cidofovir is also restricted due to its significant nephrotoxicity (1). Foscarnet and cidofovir should only be used for cases of mutant CMV strain UL97 due to their nephrotoxicity (2). Valganciclovir and valacyclovir are newer drugs currently used for treating CMV disease in transplant recipients. Both drugs can be administered orally (1). CMV treatment strategies include preemptive therapy and prophylaxis (18). Preemptive therapy is recommended for individuals with CMV viremia, while prophylaxis is preferred when the transplant donor is seropositive and the recipient is seronegative (D+, R-). High-risk patients should undergo prophylactic treatment, while low to moderate-risk patients should receive preemptive treatment (2).

**Epstein-Barr virus (EBV):**

Over 90% of adults are seropositive for EBV infection, and the initial infection is usually asymptomatic but can present as mononucleosis in adults. This virus is transmitted through saliva and close contact and is responsible for infectious mononucleosis, Burkitt's lymphoma, nasopharyngeal carcinoma, and post-transplant lymphoproliferative disease (PTLD) (1). Clinical manifestations of EBV infection in transplant recipients include infectious mononucleosis, hepatitis, pneumonia, lymphadenopathy, hepatosplenomegaly, digestive disorders, and PTLD (2, 19). The greatest risk for severe EBV illness in transplant recipients is PTLD. The frequency of PTLD is estimated to range from 0.5 to 23% in organ allograft recipients (1). PTLD is less common in kidney transplants compared to pancreas, liver, heart, lung, and intestinal transplants. Risk factors for PTLD include transplanted organ type, EBV serological mismatch between donor and transplant recipient (D+, R-), and the type of immunosuppressive therapy (2, 20).

Serology tests are useful in identifying past EBV infections (21). Due to the increase in viral load before the appearance of clinical symptoms, quantitative PCR methods are useful for detecting EBV and can help identify PTLD (1, 20).

PTLD can be treated by reducing the use of immunosuppressive drugs, surgery, radiotherapy, immunotherapy, or chemotherapy (2). Acyclovir or ganciclovir and intravenous immunoglobulin (IVIG) and rituximab (anti-CD20 antibody) are also used to treat EBV-induced PTLD, EBV-specific CTLs can also be used as therapy to manage PTLD (1, 5).

**Human herpes viruses 6 and 7 (HHV6,7):**

HHV-6 isolates are classified into two variants, HHV-6A and HHV-6B. HHV-6B is the main cause of exanthema subitum (Roseola infantum, sixth disease), whereas HHV-6A is not linked to any known disease. HHV-7 has no association with any known disease, although it has been reported to be responsible for some cases of exanthema subitum. Infection typically presents

with fever, and in some cases, respiratory distress and seizures may occur (1, 3). Both HHV-6 and HHV-7 replicate primarily in T cells, and HHV-6 also infects B cells, NK cells, and monocytes. Primary infection with these viruses occurs in early childhood, and therefore more than 90% of adults are seropositive. HHV-6 reinfection occurs in 38-60% of bone marrow transplant recipients, 22-54% of liver transplant recipients, and 23-50% of kidney transplant recipients (1, 22). The prevalence of reactivation of HHV-6 ranges from 20 to 82%, while the prevalence of HHV-7 ranges from 0 to 46% in solid organ recipients. Early infection with these viruses occurs 2 to 4 weeks after receiving the transplant, while delayed infection can occur several months to years later (22). Reactivation of HHV-6 is associated with CMV disease in bone marrow, liver, and kidney recipients (3, 22). Reactivation of HHV-6 after transplantation is usually asymptomatic but sometimes presents with skin rash, encephalitis, seizures, pneumonia, bone marrow suppression, hepatitis. HHV-6,7 can cause chronic allograft nephropathy (22).

The detection of each of these viruses can be done by directly isolating the infectious virus from the culture medium or by detecting the viral DNA by the molecular PCR method (1).

In kidney transplant recipients, ganciclovir and valganciclovir are the treatments of choice for CMV and HHV-6, and foscarnet can be used to treat HHV-7 (18). In kidney transplant recipients, ganciclovir prophylaxis, which is used to prevent the occurrence of HCMV, can also be effective in preventing HHV-6 (22).

**Human herpesvirus 8 (HHV8):**

This virus causes Kaposi's sarcoma (KS), a body cavity lymphoma, and some forms of multicentric Castleman disease (an overgrowth of cells in the lymph nodes). KS is observed in solid organ transplant recipients with a prevalence of 0.5 to 5%, depending on the patient's country of origin. The difference between the frequency of KS and the seroprevalence of HHV-8 in transplant recipients indicates that most HHV-8 reactivations or primary infections in this population do not lead to clinical disease (1). The global incidence of KS per 100,000 population per year has been reported to be 96 cases in the kidney, 49 cases in the heart, 44 cases in the liver, and 11 cases in lung recipients (5). The prevalence of the virus in the Middle East ranges from 5% to 20%, with kidney transplant recipients in Iran experiencing a prevalence of over 35%. The risk of KS after an organ transplant is 200-500 times greater than in the general population. In the Middle East, KS is the most common cancer seen in kidney transplant recipients. Symptoms may involve fever, hepatosplenomegaly, lymphoid hyperplasia, pancytopenia, and liver dysfunction (5, 23). The global incidence of KS per 100,000 population per year has been reported in 96 cases in the kidney, 49 cases in the heart, 44 cases in the liver, and 11 cases in lung recipients. In the Middle East, the virus prevalence ranges from 5% to 20%, with kidney transplant recipients in Iran having a prevalence exceeding 35%. The risk of KS post-organ transplant recipients is 200-500 times higher than in the general population. Among kidney transplant recipients in the Middle East, KS stands as the most common malignancy. Clinical symptoms encompass fever, hepatosplenomegaly, lymphoid hyperplasia, pancytopenia, and liver dysfunction.

HHV-8 is not present in the healthy general population (prevalence is between 2% and 10%), so IFA and ELISA serological assays are more useful than other methods in diagnosing primary infections. Serology is also the most accurate method for determining prior HHV-8 infection in kidney transplant recipients because viral DNA is not usually found in circulating lymphocytes of seropositive individuals (1). Definitive diagnosis is made by histopathology method (24).

Reducing the use of immunosuppressive drugs, chemotherapy, radiotherapy, and doxorubicin administration are among the treatment methods of KS in kidney transplant recipients (24). There is strong evidence that mTORi therapy can inhibit Kaposi's sarcoma (2).

## CONCLUSION

Herpesvirus infections pose a significant challenge to the long-term survival of kidney transplants, and the increase in the incidence of these infections can also increase the risk of rejection and malignancy after kidney transplantation. Prevention and treatment of

herpes diseases depend on a limited number of antiviral drugs, and registered vaccines are available only against VZV. This article emphasizes the importance of understanding the risk factors, diagnostic methods, and prevention and management strategies for these infections in the pre and post-transplant periods.

## ETHICAL APPROVAL

Not required

## COMPETING INTERESTS

None declared

## AUTHOR CONTRIBUTION:

SSM: Drafting the review article, editing, revision, and supervision of the manuscript writing process. MEK: Editing and drafting the review article. MGB, AY: Data gathering, Review & Editing

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