Herpes Viruses in Transplant Recipients: HSV, VZV, Human Herpes Viruses, and EBV

Kevin Shiley, MD*, Emily Blumberg, MD

KEYWORDS

• Herpes virus • PTLD • Kaposi sarcoma
• Zoster • HHV-6 • HHV-7

The herpes viruses comprise a large group of enveloped DNA-containing viruses that characteristically cause latent infection in their respective hosts. There are 8 known herpes family viruses associated with human infection: herpes simplex virus (HSV) types 1 and 2, varicella zoster virus (VZV), Epstein-Barr virus (EBV), *Cytomegalovirus* (CMV), *Human herpesvirus 6* (HHV-6), *Human herpesvirus 7* (HHV-7), and *Human herpesvirus 8* (HHV-8). Of these, CMV has received the most attention as a cause of morbidity and mortality among transplant recipients and is discussed separately in articles by Ljungman, Strasfeld, Hirsch, and Einsele in this issue. The remaining herpes viruses are also responsible for significant disease in the transplant patient population. The role of each of these viruses as a cause of disease in the transplant population is discussed in this article.

HSV-1 AND HSV-2

The α-herpes viruses, HSV-1 and HSV-2, are responsible for oral and genital mucocutaneous ulcers in the general population. HSV-2 is generally considered to be sexually transmitted and primarily infects the urogenital mucosa, whereas HSV-1 predominantly affects the oral mucosa and is often transmitted through nonsexual contact.

Dr Shiley has no financial disclosures.
Dr Blumberg receives financial support from Roche Pharmaceuticals for research support and consulting services. She also receives research support from Viropharma as a site investigator in a multicenter trial.
Division of Infectious Diseases, Hospital of the University of Pennsylvania, 3rd Floor Silverstein Pavilion, Suite E, 3400 Spruce Street, Philadelphia, PA 19104, USA
* Corresponding author.
E-mail address: shileyk@uphs.upenn.edu

Infect Dis Clin N Am 24 (2010) 373–393
doi:10.1016/j.idc.2010.01.003 **id.theclinics.com**
0891-5520/10/$ – see front matter

Both viruses are neurotropic and primarily infect neurons in their latent forms. Reactivation of HSV is common among transplant recipients, and is the second most common cause of viral infection after transplantation.[1–3]

Most HSV-1 and HSV-2 infections occur in the setting of reactivation rather than primary infection, although primary HSV infections are well documented, particularly among younger patients.[4] Primary infection from transplanted tissue is uncommon but has been observed in renal transplant recipients.[5,6] The high percentage of cases attributed to reactivation is undoubtedly a result of a high baseline population seroprevalence of HSV-1 and HSV-2. Seroprevalence increases with age and varies by geographic, racial, socioeconomic, and ethnic characteristics among the general population. Antibodies to HSV-1 were found in 50% to 96% of people in previous seroprevalence studies.[7–9] Analysis of Americans from the National Health and Nutrition Examination Survey showed the seroprevalence of HSV-1 to be 65% and HSV-2 to be 26% by age 49 years.[10] Higher rates of seropositivity were found in women and minorities in the same survey. The greatest risk factor for reactivation of HSV following transplantation is lack of antiviral prophylaxis.[4,11–15]

Before the introduction of acyclovir, reactivation of HSV infection was estimated to occur in up to 80% of patients receiving hematopoetic stem cell transplant.[13–15] Lower, but still substantial, reactivation rates were described in solid-organ transplant recipients in the years before effective antiviral prophylaxis.[5,16–19] The clinical manifestations of HSV infection range from limited mucocutaneous outbreaks to disseminated infections involving visceral organs and the central nervous system (CNS).

The most common manifestations of HSV are mucocutaneous outbreaks, usually involving the oral and genitourinary mucosa.[20] These infections, which can lead to extensive mucosal involvement, typically occur in the first 30 days following transplantation if prophylaxis is not administered.[1,14,15,18,21] Less common manifestations of HSV involving the lungs and viscera are also described. Pneumonia as a result of HSV-1 and HSV-2 is typically preceded by gingivostomatitis, however pulmonary involvement from disseminated infection and airway manipulation may also occur.[22–28] The diagnosis of HSV pneumonia is complicated because viral shedding within the airways is common in immunosuppressed and critically ill adults and does not necessarily reflect true pneumonia.[29–33] The use of acyclovir in critically ill patients with HSV isolated from respiratory secretions has not been shown to influence mortality, ventilator dependence, or length of hospitalization.[33,34] Therefore, caution should be taken in interpreting results from viral cultures, direct fluorescent antibody staining, and nucleic acid assays without associated cytopathic evidence of infection on tissue biopsy.

Hepatitis is an uncommon manifestation of HSV that is described in several case reports and case series.[17,35–40] When HSV presents with hepatitis there is often evidence of disseminated disease with involvement of the skin and mucous membranes.[36,39] Patients may seem well initially, with elevated liver function tests as the only sign of infection.[37] More often, patients present with nonspecific flulike symptoms of fever, malaise, and myalgias. Increasing levels of aspartate aminotransferase and alanine aminotransferase, sometimes 10 to 20 times the upper limit of normal, are often observed. Cross-sectional imaging may appear normal, but in some cases liver infiltration with microabscesses has been observed.[35] Most cases occur within 30 days of transplant, however some cases have occurred years after transplant.[40] Nearly all HSV hepatitis cases in the literature occurred in patients while off antiviral prophylaxis. Diagnosis is made by liver biopsy with culture and antibody staining for HSV-1 and HSV-2. Pathology typically reveals necrotic hepatitis with loss of lobular architecture.[38] Other visceral manifestations of HSV infection in immunosuppressed hosts include esophagitis, gastritis, and colitis.[41–48]