

Herpes Simplex Viruses 1&2 Overview

ABOUT THE VIRUS

The two herpes simplex viruses, HSV-1 and HSV-2, are linear, double-stranded DNA viruses with an icosahedral capsid. Both are members of the Herpesviridae family and Alphaherpesvirinae subfamily, along with VZV. The herpesviruses and resulting infections were first identified and demonstrated in the early 1900s. All three viruses share the ability to establish latency in their host following primary infection. HSV-1 and HSV-2 establish latency in neurons of dorsal root ganglia.

Herpes simplex virus (HSV) infections are extremely common in humans; in most cases, they are simply bothersome and frustrating. However, infections can become life-threatening for some individuals, especially those who are immunocompromised. Lethal, disseminated disease can occur in neonates if the virus is acquired during passage through an infected birth canal or through prolonged rupture of the membranes in an infected mother.



This H&E-stained micrograph depicts the histopathologic changes seen in brain tissue due to herpes encephalitis.

Image courtesy of CDC.

CLINICAL MANIFESTATIONS

Humans are the only natural carriers of HSV, which is transmitted by way of direct contact with secretions that are infected with the virus. Viral titers are higher when the infection is actively producing lesions; it is believed that risk of transmission is greater during this time, although the virus has been documented to be transmitted during periods of apparent latency. At any given time, it is estimated that HSV can be isolated from 1-5% of asymptomatic adults and 20% of asymptomatic children. Primary infections with HSV-1 most commonly involve the mouth and throat. Primary infections with HSV-2 most commonly involve the genital region, however, both viruses can infect any mucous membrane. As orogenital sexual practices have become more common, it is not unusual to see genital infections caused by HSV-1. Autoinoculation between different areas of the body, such as the eye, also occur.

Primary HSV-1 infections are often asymptomatic, but can manifest as gingivostomatitis or pharyngitis, most commonly in children under age 5. Probability and age of acquisition is inversely related to socioeconomic status. In more affluent societies, a second wave of acquisition by exchange of salivary secretions is common during adolescence. A 2-12 day incubation period is followed by fever, sore throat and pharyngeal edema with erythema.

Vesicles develop on the mucosa of the mouth and throat, which ulcerate and proliferate, often spreading to the soft palate, tongue and floor of the mouth. Lesions may appear on the face and gums are usually tender and bleed easily. Fever, toxicity and severe pain may linger for several days, but the infection usually runs its course within 10-14 days. Encephalitis is an unusual manifestation of HSV; HSV-1 is most often responsible, except in the case of neonates. If left untreated, the case fatality rate is approximately 70%, with survivors suffering significant neurologic sequelae.

Primary HSV-2 infections are also often asymptomatic, but significant disease often occurs, particularly in females. Genital HSV infections are manifested as ulcerating vesicular lesions on the vulva, vagina, cervix, urethra, and perineum in females, on the penis in males and the rectum and perianal region in homosexual males. Symptoms can include inguinal lymphadenopathy, pain, itching, swelling, discharge and dysuria; systemic symptoms include fever and malaise. Meningitis also occurs in about 10% of cases. Initial disease will often be less severe if antibodies are present from HSV-1.

Following initial infection, a lifetime viral latency is established in nearby nerve ganglia. Reactivation occurs with varying frequency, depending upon the individual. Reactivation is often preceded by a prodrome consisting of hyperesthesia.

Immunocompromised patients have a greater risk of developing severe, disseminated HSV infections. Immunocompromised patients can include solid organ transplant patients, bone marrow transplant patients, HIV patients, burn victims and neonates. Transplant patients often excrete HSV in throat washings during the initial weeks following transplantation. For this reason, transplant patients are often prophylaxed with acyclovir. Typical infections are respiratory or gastrointestinal in nature and involve tracheobronchitis, pneumonia, esophagitis and hepatitis.

Neonatal herpes is a very serious disease; prior to the use of acyclovir, it was often fatal. Infants acquire neonatal herpes by passing through an infected birth canal or through prolonged rupture of the membranes in an infected mother. If the mother has a primary infection at the time of delivery, the neonate has a 30-40% risk of acquiring the virus. If the mother has a recurrent infection at the time of birth, the risk of neonate infection is much lower, around 3-4%. The viral infection can be manifested as encephalitis or disease localized to mucocutaneous surfaces, such as skin, eyes and mouth. If untreated, neurological disease carries a high fatality rate, with survivors experiencing severe neurological sequelae. Local disease in the neonate can progress to severe disseminated disease, if left untreated.

LABORATORY DIAGNOSIS

Culture of HSV was the mainstay of diagnosis for many years, as the virus grows easily in a wide variety of cell lines in vitro. However, the temperature lability of HSV was a significant limitation of culture. If the time delay between collection and arrival in the laboratory was too great, the virus would no longer be infectious, resulting in a false negative culture. In addition, HSV will not grow from CSF samples, yet another significant limitation of culture. With the advent of molecular detection methods, analysis of CSF for HSV DNA quickly became the preferred method of diagnosis when ruling out HSV meningitis. Real-time quantitative PCR has become a powerful diagnostic tool for many clinical situations, as it allows determination of a patient's viral burden (viral load) in a given sample. As a result, clinicians are able to track response to interventions, such as administration of acyclovir.

TREATMENT

Acyclovir has been used in the treatment of HSV infections for about 30 years. It is highly specific for herpesvirus-infected cells and has an acceptable safety profile. The development of valacyclovir offers similar clinical and safety benefits, with a simpler treatment regimen. Acyclovir and valacyclovir have been studied for the treatment of HSV infections in bone marrow and renal transplant patients, as well as individuals with HIV. Both drugs have been effective in each of these groups. In immunocompromised patients, acyclovir is helpful for both treatment and suppression of recurrent lesions. This is true for transplant recipients, leukemics undergoing chemotherapy and AIDS patients. Acyclovir has also proven invaluable in treatment of neonates with HSV infections.

Selected References

Griffiths PD. Tomorrow's challenges for herpesvirus management: potential applications of Valacyclovir. *J Infect Dis.* 2002;186 (suppl 1):S131-137.

Hirsch MA. Herpes simplex virus. In: Mandell GL, Bennett JE, Dolin, eds. *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases.* Vol 2. 4th ed. New York, NY: Churchill Livingstone; 1995:1336-1345.

Knipe D, Howley P. *Fields Virology.* 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.

Simmons A. Clinical manifestations and treatment considerations of herpes simplex virus infection. *J Infect Dis.* 2002;186(suppl 1):S-71-77.

Tang Y-W, Mitchell PS, Espy MJ, Smith TF, Persing DH, et al. Molecular diagnosis of herpes simplex virus infections in the central nervous system. *J Clin Microbiol.* 1999;(37):2127-2136.

Whitley RJ, Roizman B. Herpes simplex virus infections. *Lancet.* 2001;(357):1513-1518.

