

Diagnosis of Herpes Simplex Virus Infections

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Introduction

Herpes Simplex Virus (HSV) causes superficial and systemic infections within every major organ system of the body in both normal and immunocompromised patients. Severity of infection may range from mild to severe disease. Site of infection may include the skin, lips, oral cavity, eyes, genital tract and central nervous system¹.

Two distinct HSV genotypes exist, HSV-1 and HSV-2. HSV-1 is considered to be primarily associated with ocular and oral infection, while HSV-2 is considered to be associated with genital infection. However, it is now known that either strain of HSV may be isolated from herpetic lesions and can cause genital herpes^{1,2}.

It is estimated that 500,000 to 1 million people acquire HSV infection each year, and at least 50 million individuals in the United States have genital herpes infection. Genital herpes causes a wide variety of signs and symptoms ranging from classically painful vesicles/ulcers to the atypical, including urethritis, cervicitis, and skin or mucosal itching, burning, or tingling. Genital herpes is often undiagnosed because of its wide range of symptoms. About 60% of people infected have un-recognized or nonspecific symptoms. However, all people infected with HSV-2, regardless of a history, usually have episodes of asymptomatic viral shedding. Accurate diagnosis and genotyping of the virus is necessary for the treatment of the infected patient, for reduction and prevention of the transmission of HSV to a sexual partner, and for reduction and prevention of HSV transmission to a neonate¹.

Genital herpes can be difficult to diagnose on the basis of presentation and patient history. According to the 2002 US Center for Disease Control and Prevention (CDC) STD recommendations, diagnosis of genital herpes should be confirmed by laboratory testing¹.

Tests available for diagnosis of HSV infection

Traditionally, the laboratory test used most often for the diagnosis of HSV infection has been viral culture because it is highly specific, widely available, and relatively inexpensive. Viral culture can be useful in women presenting with new or recurrent genital ulcer disease. However, even with a primary infection, viral culture is insensitive, with a false negative rate of up to 25%. In recurrent disease, the rate of viral isolation is less than 50%^{1,2}. This low rate of viral isolation resulted in the need for a more sensitive test for detection of HSV infection.

Polymerase chain reaction (PCR) is highly sensitive and specific, and it can be used to detect the virus even during the low viral shedding phase. Several studies have demonstrated that its sensitivity is 1.5 to 4 times greater than viral culture⁴. Based on ACOG's 2004 recommendation, **PCR is the test of choice in the diagnosis of herpes-related infections**. Because samples for PCR testing are easier to obtain and more stable than samples for viral culture, PCR testing is likely to replace viral culture for the diagnosis of HSV genital infection in the future¹.

Antigen detection tests (DFA) are also available which are comparable to the performance of viral culture but they do not distinguish between HSV-1 and HSV-2 infection².

In addition to these methods, the detection of type-specific antibodies to HSV-1 and HSV-2 can also help to establish a diagnosis. Antibodies to HSV-2 are detected 2 to 12 weeks after acquisition of infection and persist indefinitely². Only tests that are based on the detection of antibody response to glycoprotein G-2 for HSV-2 and glycoprotein G-1 for HSV-1 are type specific. ELISA, based on whole-antigen preparation (whole viral lysate), is not a preferred testing method because often it cannot differentiate between HSV-1 and HSV-2^{1,2,3}. It is important to know that serology testing has its limitations. Serology testing will not indicate the site of infection or the stage of the infection. It will not differentiate between a current or past infection and there is an increased risk of false negative results if the testing is done too early. Serologic testing for HSV-1 is even less helpful because a positive test may result from prior infection (more than 50% of people are infected with HSV-1 during childhood). Another limitation of serologic testing is its low specificity, which results in an increased risk of false positive results^{1,2}.

Recommendations for diagnostic testing for HSV infection

Genital lesions suspicious for herpes should have laboratory confirmation. Culture or PCR should be performed if lesions are present. Antigen detection can be nearly as sensitive as culture method, however, it is not as sensitive as PCR and it cannot genotype.

If no lesion is present, or patient has HSV culture-negative recurrent lesions, PCR should be offered, as PCR has ability to detect the virus during the viral shedding. If PCR is negative HSV serology should be offered to aid in diagnosis. Absence of antibodies may rule out genital herpes as the cause of the lesions or ulcerations, whereas presence of antibody might confirm the diagnosis.

If patient is asymptomatic (but has been exposed or requires testing for any other reason) serology testing should be performed.

Pregnant women who have primary HSV infection close to the time of delivery are at high risk for vertical transmission to their fetus.

Viral culture or PCR have been recommended to identify women at risk of acquiring genital HSV-1 or HSV-2 infection close to term. Serology screening could be used in women whose sexual partners have a history of recurrent genital herpes, testing can determine whether or not they are at risk of primary infection by testing for seroconcordance.

In addition, pap-smear may be used as a screening tool in evaluation of Herpes.

Recommended Use of Diagnostic Tests for Diagnosis of HSV Infection	Culture	PCR	Serology Testing
Symptomatic patients with lesions	Yes	Yes	Yes
Symptomatic patients without lesions		Yes	Yes
Recurrent infection with lesions	Yes	Yes	
Recurrent infection without lesions		Yes	
Pregnant women with the history of HSV infection		Yes	
Pregnant women without the history of HSV infection exposed to a partner with history of HSV			Yes
Asymptomatic patient exposed to a partner with history of HSV infection			Yes
Patients with high risk of STD		Yes	Yes

References:

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4. Wald A, Huang ML, Carrell D, Selke S, Corey L. Polymerase chain reaction for detection of herpes simplex virus (HSV) DNA on mucosal surfaces: comparison with HSV isolation in cell culture. *J Infect Dis.* 2003 Nov 1;188(9):1345-51. Epub 2003 Oct 31.