

Herpes Diagnostics

With newer, sophisticated DNA tests complementing type-specific blood tests and viral culture, the array of herpes simplex virus (HSV) diagnostic options is more complex than ever. In this expert Q&A, Leandro Mena, MD, MPH, and James B. Brock, MD, of the University of Mississippi Medical Center explain the best uses of the different tests for herpes that are available to diagnose patients with and without symptoms.



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Viral culture tests

Viral culture tests for herpes simplex virus (HSV) are done by taking a swab directly from sores and blisters that are part of a suspected herpes outbreak. The samples are grown in a lab, and can be typed to distinguish HSV-1 from HSV-2.

Q: An HSV culture is usually the test of choice for patients with symptoms, like classic herpes sores. While a culture for HSV is reliable if positive, can't there be issues with false negatives if the sores are healing or crusting over?

A: Yes, culture has been the traditional method for diagnosis of herpes simplex infections. However, viral culture is typically only positive in early lesions, and they are not very useful once lesions begin to heal. If a culture is performed on a healing lesion and is negative, you may still have a herpes infection. Use of culture is very low if no active lesions are present. Herpes virus can be cultured from more than 90% of fluid-filled lesions, but ulcers can be cultured only 70% of the time, and only 27% can be cultured at the crusting stage.^{1,2}

How reliable is an HSV culture test during an initial outbreak versus, say, a recurrent episode?

Viral culture is much more reliable during a first-time infection, rather than a recurrent infection because the amount of virus present is much higher. Even in an initial outbreak, though, a negative culture does not mean that you absolutely do not have a herpes infection.

Do labs automatically type an HSV culture for HSV-1 and HSV-2? Given that genital HSV-1 is increasingly common, is this a discussion patients need to have with their provider to make sure they receive this information?

If herpes simplex virus is isolated in viral culture, it should be routinely typed. Patients have a right to their laboratory information, and HSV typing may be useful to know because HSV-2 is more likely to cause recurrent genital herpes.

DNA Tests

Similar to viral culture tests, HSV DNA tests involve taking a sample directly from a suspected HSV sore. These tests detect the genetic material (DNA) of HSV.

The most common DNA tests used in clinics to diagnose HSV are polymerase chain reaction (PCR) tests. They work by taking a tiny amount of the HSV DNA and multiplying the material to make many, many copies so the lab can tell that herpes is present. This test has become very useful in special situations, too, such as HSV infections of the brain and surveillance testing of newborns born to mothers with genital herpes infection.

How do PCR tests for HSV stack up to culture tests?

PCR is 3-4 times more likely to isolate herpes simplex than viral culture. When sores are healing or absent, PCR may still be able to isolate virus when culture is not very useful. Also, viral culture requires proper handling of specimens by keeping them cold and processing them soon after sampling, which is not as much of an issue with PCR. PCR can also be run much more quickly (2 hours), whereas culture requires several days to grow.

Why aren't HSV PCR tests used more commonly in clinics?

Viral culture remains a recommended test-of-choice along with PCR. PCR is a newer test and may be more costly. Physicians may also be unaware that PCR for HSV is available and more likely to isolate the virus.

Blood Tests

In addition to isolating herpes simplex virus by culture or DNA methods, antibodies against HSV (serology) can be detected by a simple blood draw. A positive antibody test indicates prior exposure to the virus and thus infection. However, it cannot completely tell you that a suspicious lesion is caused by herpes, which requires a sample that isolates the virus itself.

If you have no active lesions when you see your doctor, though, viral culture and PCR are of limited use, and antibody testing may be the only test that can be run. Viral antibodies will be tested for both HSV-1 and HSV-2. Since HSV-2 is almost always transmitted sexually, a positive HSV-2 antibody test is useful for sexual risk reduction counseling.

Let's talk about just who is a good candidate for an HSV blood test. Would you comment on the value of routine HSV testing with patients who have a history of symptoms but who have never been diagnosed?

In patients with no active lesions, PCR and culture are of limited value. Negative antibodies to HSV-1 and HSV-2 may be useful to argue against HSV infection as the cause of those symptoms. However, most individuals have HSV-1 antibodies and are difficult to interpret. A positive antibody test to HSV-2 would suggest genital herpes infection as the cause of the symptoms.

What about blood tests for someone with a current or recent partner who has HSV-2?

If your partner has HSV-2, serology may be useful to know whether or not you have been exposed in the past to HSV. A negative antibody test to HSV-2 would suggest that you are at risk for future infection with HSV-2 if you have an infected partner.

Should pregnant women be tested for HSV?

Transmission of herpes to newborns is highest in women with recent HSV infection. Therefore, pregnant women with negative serology would be considered at risk for HSV infection and should be counseled to abstain from sex in the third trimester with a partner known to have herpes. However, the same recommendation is applied to pregnant women not known to have clinical herpes without serologic testing.

What about routine HSV testing for those who are HIV-positive or in a relationship with someone who has HIV?

HSV infection in HIV-infected patients, especially those

with weakened immune systems before start anti-retroviral therapy, tends to be more severe and more prolonged, and recurrent HSV infection is more common in HIV-infected patients. If an HIV-infected patient has positive serology for HSV-2, suppressive antiviral therapy may be offered to prevent HSV recurrence. Also, patients with genital herpes are at increased risk for HIV infection, and the risk is still increased even with antiviral treatment for HSV. Treatment of the HIV-infected partner with HIV antiretrovirals, however, would be expected to decrease HIV transmission.

Are there other populations that might benefit from testing?

Screening by HSV serology for patients that are high risk for infection, including those with multiple sexual partners and men who have sex with men (MSM), can be considered. A negative HSV-2 serology would suggest future risk for infection with HSV-2. Also, patients with recurrent genital symptoms and a negative HSV culture or PCR may have serologic testing performed. Negative HSV-2 serology would make genital herpes less likely.

HSV blood tests are based on detecting antibodies, which take a few weeks or even months to develop at detectable levels. How long should someone wait to be tested?

If a patient feels that they were recently exposed, acute (now) and convalescent (later) serology can be obtained. Negative results now and positive results in 4-6 weeks would suggest a recent infection with HSV.

When someone receives results from their HSV blood test they're given a number called an index value (measuring the antibody levels detected). This is a huge source of confusion for patients who have intermediate or "low positive" index values (people often contact us and say "My values are 3.2 so do I have herpes or not?"). What are the numerical cut-offs for when you feel confident that someone has a solid positive or negative HSV blood test result?

An index value less than 1.1 should be considered negative, and above 3.5 should be considered positive.

So when somebody has a hazy test result, a so-called low positive, talk about confirmatory testing. How long should they wait and which test(s) should be used?

Index values in the middle range are difficult to interpret, as false positives and false negatives can occur in

this range. If a “low positive” index value is encountered, testing can be repeated with another method, including the Western Blot, Biokit Rapid assay, and the Focus recombinant inhibition HSV-2 ELISA (from Quest). Also, those with recent infection may not have had time to develop antibodies. By 3 weeks, about half of infected individuals will have detectable antibodies, 70% by 6 weeks, and almost 100% by 6 months. Waiting 6 months should be sufficient time to allow for antibody production.

Please explain the difference between HSV IgG tests and IgM tests: how does this figure into the idea of a type-specific HSV blood test?

IgM antibody is usually the first antibody that is produced by the body during an infection and tends to decrease over time. On the other hand, IgG levels increase weeks after an infection but may remain positive for years to life.

Should HSV IgM tests ever be used clinically?

IgM antibody does not distinguish HSV-1 from HSV-2 infection and is not very useful clinically.

Can an HSV blood test ever distinguish a recent from a longer-standing infection?

Positive antibody tests indicate exposure and may remain positive for life. If a patient has had a negative antibody test in the past and now has a positive antibody, then the exposure likely occurred between the time of those two tests. A negative antibody test now and a

positive antibody test in the near future suggests a recent infection.

What about the value of HSV-1 testing? Many adults have HSV-1 in the way of oral herpes they may have experienced since childhood. An increasing number of genital herpes infections are due to HSV-1 though. When is there value to having an HSV-1 blood test?

It is true that most adults will have a positive HSV-1 antibody test. This does not help to distinguish prior exposure from current infection with HSV. A negative HSV-1 antibody test may or may not be reliable depending on the type of test that was done, particularly the HerpeSelect HSV-1 ELISA. However, a negative HSV-1 antibody by another assay may suggest risk for infection with HSV-1 in the future. HSV-1 isolated by culture or PCR in a genital site is strongly suggestive of HSV-1 genital herpes, on the other hand.

How often does HSV-1 and HSV-2 co-infection occur at the same site? Are there any implications here regarding testing?

It is unclear how often HSV-1 and HSV-2 infection occurs at the same site, but genital HSV-1 infection rates are increasing and may account for up to 50% of new genital herpes infections now. However, it is much less likely to cause recurrent genital herpes, and HSV-2 accounts for about 90% of recurrent genital herpes infections. If a patient has recurrent genital herpes and positive serology for HSV-1 and HSV-2, it is likely that HSV-2 is the culprit of the recurrent genital herpes.

Resources

ASHA's Herpes Resource Center
Herpes Testing Toolkit
University of Mississippi Medical Center

References

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.* Nov 1 2003;188(9):1345-1351.

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