



Herpes simplex virus serology in an asymptomatic patient



Belinda Sheary, BMed, is a general practice registrar, Charlestown, New South Wales. bsheary@hotmail.com

Linda Dayan, BMedSc, MBBS, MM (SexHlth), DipRACOG, MRCMA, FACSH, is Director, Sexual Health Services, Northern Sydney Health, Head, Sexual Health Department, Royal North Shore Hospital, Clinical Lecturer, Department of Public Health and Community Medicine, University of Sydney, and a general practitioner, Sydney, New South Wales.

BACKGROUND

Genital herpes is one of the most common sexually transmitted infections. While genital herpes can present with self limiting genital lesions, most people with genital herpes simplex virus (HSV) infection are asymptomatic or have unrecognised infection. Use of type specific serology for HSV antibodies can identify these individuals.

OBJECTIVE

This article discusses the role and use of HSV serology in asymptomatic patients, including pre- and post-test counselling and interpreting results.

DISCUSSION

The indications for HSV serology in an asymptomatic patient are limited. Patients tested for HSV antibodies require careful assessment and counselling. Identifying asymptomatic genital herpes should ideally only be done in cases where there may be clinical benefit. Limitations of type specific HSV serology need to be considered when interpreting the results in low risk patients.

Genital herpes is one of the most common sexually transmitted infections (STIs) in Australia. It can be due to either HSV-1 or HSV-2 infection. HSV-1 genital herpes is associated with infrequent outbreaks.¹ HSV-2 is responsible for the majority of recurrent genital herpes.²

Most people with genital HSV infection are either asymptomatic or experience 'unrecognised' symptoms, and so genital HSV infection often remains undiagnosed. Genital herpes remains stigmatised despite relatively minor physical morbidity and the availability of effective treatment to manage symptoms.

Type specific HSV serology has been used in research settings to estimate the prevalence of HSV antibodies in different populations. In clinical practice, a diagnosis of asymptomatic HSV infection may result in greater patient harm than benefit. In symptomatic patients, a direct detection test from the lesion via culture, nucleic acid tests (NAAT) such as polymerase chain reaction (PCR), or antigen testing (IF) is preferable as they are site specific.

Epidemiology of HSV antibodies

HSV-1

HSV-1 seropositivity can indicate either oro-pharyngeal or genital infection.^{3,4}

Up to 80% of Australian adults are HSV-1 seropositive,⁵ with only a third reporting ever having a 'cold sore'.⁵ HSV-1 genital herpes may be increasing in incidence, especially in younger people. In a Melbourne study, the proportion of first episode genital herpes due to HSV-1 increased from 15.8 to 34.9% of cases between 1980 and 2003.⁶ The rising incidence of HSV-1 genital herpes could be the result of decreasing HSV-1 seroprevalence and consequently a larger susceptible population and/or an increase in the popularity of oral sex.

HSV-2

The presence of HSV-2 antibodies essentially confirms genital HSV infection^{4,7} as oral HSV-2 is uncommon without concomitant genital infection.⁴ HSV-2 seroprevalence has ranged from 11–65% in Australian based studies.^{5,8,9} Prevalence is higher in females, and increases with age and number of sexual partners.¹⁰

Less than 25% of HSV-2 seropositive people report a clinical diagnosis of genital herpes.^{5,8,9} Unrecognised infection is common, however studies demonstrate that 50–60% of 'asymptomatic' HSV-2 seropositive people can identify clinical outbreaks after an educational session.^{11,12}

Role of HSV serology in the asymptomatic patient

Sexual health screening

The Australian Herpes Forum Management group advise against the use of HSV serology in asymptomatic people.¹³ In asymptomatic HSV infection there is often no direct benefit in making the diagnosis as there is no cure and the infection is life long. Harm to the patient may take the form of psychosocial morbidity¹⁴ with HSV-2 positive patients often concerned about potential transmission to sexual partners. While abstinence during clinical outbreaks, condoms and antiviral therapy may reduce the risk of transmission in symptomatic infection, absolute elimination of risk is not possible.

In a study of HSV serodiscordant couples advised to abstain from sexual contact during HSV recurrences, transmission occurred in 3.8% and 16.9% of susceptible male and female partners respectively over 12 months.¹⁵ Condoms offer significant protection against male to female transmission of HSV, but not vice-versa.¹⁶ Suppressive antiviral therapy with valaciclovir reduces HSV transmission by almost 50%.¹⁷ However, the Pharmaceutical Benefits Scheme (PBS) restricts the use of antiviral medications to people with moderate to severe recurrent genital herpes confirmed via a direct detection test. (Microbiological confirmation is not required in cases where suppressive treatment was commenced before May 2004).

It has yet to be established whether there is a public health benefit in identifying asymptomatic people infected with HSV. However despite this, and the difficulties discussed above, patients may still want to be tested. Studies have shown a wide range of acceptance rates for HSV serology in asymptomatic patients. In one study, less than 40% of sexual health clinic patients agreed to be tested for HSV,¹⁸ while in another, over 90% said they would want to know if they had the infection.¹⁹

Asymptomatic partner

Patients may want to know their HSV status

after learning a partner has been diagnosed with genital herpes. The Australian Herpes Management Forum suggest testing in this situation may provide useful information and enable appropriate counselling regarding a partner's risk of acquiring HSV infection.¹³ Pre-test counselling and estimating the pre-test probability is essential.

Pre-test counselling

Pre-test counselling for HSV serology aims to provide the patient with sufficient information to give informed consent and prepare the patient for either a positive or negative result. Exploring the reasons behind a patient request for HSV serology may uncover pertinent information, helping to tailor counselling to the individual. Patient anxiety, if present, needs to be addressed. The relatively minor nature of this common viral skin infection and its lack of serious physical sequelae should be emphasised. Pre-test discussion could also include information on HSV prevalence and the proportion of infected people with asymptomatic genital herpes and discussion of the limitations of serology tests.

Significance of HSV serology results

If HSV-2 positive, the result may impact on the patient's current or future relationships, as disclosure (and sometimes nondisclosure) to partners can create anxiety. Risk of transmission to a partner cannot be eliminated

and antiviral therapy for asymptomatic carriers is not indicated or available as a subsidised benefit on the PBS.

A HSV-2 negative result indicates the patient is at risk of acquiring the infection, and it is important to explain this risk cannot be eliminated (although condoms provide women with some protection). If patients test positive for HSV-1 they could potentially infect a partner with HSV-1 genital herpes by performing oral sex if their partner is HSV-1 seronegative. If they test negative for HSV-1 they are at risk of acquiring HSV-1 genital herpes through receptive oral sex.

Interpretation of serology results

Table 1 provides an overview of the terminology used in evaluating diagnostic tests. Accurate interpretation of a HSV serology result requires consideration of the patient's sexual history (plus examination findings, if relevant) and the type of test used.

Clinical history and examination

When requesting HSV serology, an adequate sexual history is important to evaluate the pre-test probability of a positive result. Pre-test probability is the perceived probability of a diagnosis in a patient by a clinician. The number of lifetime sexual partners and a history of genital lesions suggestive of HSV infection are both risk factors.² Having a current or previous partner with genital

Table 1. Overview of terminology used in evaluating diagnostic tests

	Disease present	Disease absent
Test result positive	True positive (TP)	False positive (FP)
Test result negative	False negative (FN)	True negative (TN)
Sensitivity is the proportion of people with the disease who test positive. Sensitive tests enable a diagnosis to be 'ruled out' when the result is negative. Sensitivity = TP/(TP+FN)		
Specificity is the proportion of those without a disease who test negative. Specific tests enable a diagnosis to be 'ruled in' when the result is positive. Specificity = TN/(FP+TN)		
Positive predictive value is the proportion of people with a positive result who truly have the disease. Positive predictive value = TP/(TP+FP)		
Negative predictive value is the proportion of people who test negative who truly do not have the disease. Negative predictive value = TN/(FN+TN)		

herpes is also significant, with HSV-2 seroprevalence ranging from 35–70% in this population.^{5,7,17} Clinical examples of varying pre-test probability are shown in *Figure 1*.

Type of test used

Western Blot

Western Blot is regarded as the gold standard for HSV serology,¹⁸ however, as it is an expensive and labour intensive test, it is performed in only a few reference laboratories. There may be a direct cost to the patient.

Glycoprotein G based type specific test

Enzyme linked immunosorbent assays (ELISA) based on the type specific antigen glycoprotein G (gG) are commercially available; gG-1 and gG-2 differentiate HSV-1 and HSV-2. Although the sensitivity and specificity of glycoprotein G tests is high, the positive predictive value can be poor in low prevalence populations. This problem is illustrated in *Figure 2*, which uses the example of a test with 96% sensitivity and 97% specificity. Stated in another way, the test has an unacceptable rate of false positives when used in low prevalence populations (*Figure 3*). Hence patients who test positive and have a low pre-test probability for HSV-2 antibodies may be advised to have a Western Blot to confirm the result.²

Post-test counselling

Reiteration of some of the issues discussed in pre-test counselling may be required. Normalisation of HSV infection is important, so reinforcing the high prevalence of HSV is appropriate. The morbidity associated with genital herpes for many people is mostly psychosocial – not physical, and so the stigma of genital herpes should be addressed.

Role in couples planning pregnancy

Neonatal herpes

Screening pregnant women and their partners for HSV antibodies to prevent neonatal herpes is not considered cost effective in a low prevalence population.²⁰ Neonatal herpes is rare in Australia, with an

Low pre-test probability		High pre-test probability	
18 year old man	29 year old woman	42 year old divorced	45 year old woman
2 lifetime sexual partners, neither with known genital herpes, condoms used for contraception, asymptomatic	6 lifetime sexual partners, inconsistent condom use, new partner has genital herpes, asymptomatic	male, 10 lifetime sexual partners, ex-wife of 17 years had genital herpes, has never used condoms, asymptomatic	estimates >30 lifetime sexual partners, history of recurrent genital lesions, diagnosed as having genital herpes by previous GP

Figure 1. Pre-test probability for HSV-2 seropositivity

estimated incidence of 3.2/100 000 births.²¹ It can be secondary to HSV-1 or HSV-2, and is the most serious potential complication of HSV infection, with high mortality and morbidity.²² The risk of neonatal herpes is less than 1% in women with known genital herpes.²³

Potential indication in an asymptomatic pregnant woman

A pregnant woman with a sexual partner with known genital herpes may request HSV serology to determine if she is at risk of acquiring HSV during the pregnancy. It may be appropriate in this clinical scenario to screen for HSV antibodies, as the risk of neonatal herpes is 30–50% in babies born to women who acquire HSV shortly before labour,^{22–24} and feasible measures can be taken to minimise this risk.

Implications of HSV antibody status in a pregnant woman

If a woman is HSV-2 seropositive, she can be reassured the risk of neonatal herpes is low, as discussed above. If she is HSV-2 seronegative, sexual partner/s should also be tested. If a sexual partner is HSV-2 seropositive, she may be advised to abstain from penetrative sex during the third trimester or practise ‘safe’ sex.^{23,24} HSV-2 positive partners could be prescribed suppressive therapy with valaciclovir (although this will require a private prescription unless PBS

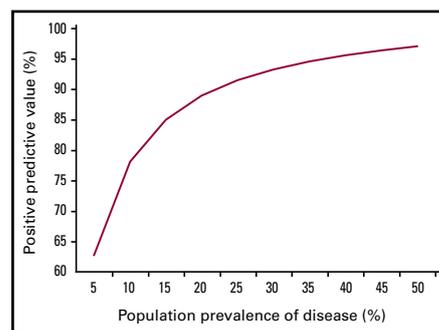


Figure 2. Positive predictive value of a test with 96% sensitivity and 97% specificity

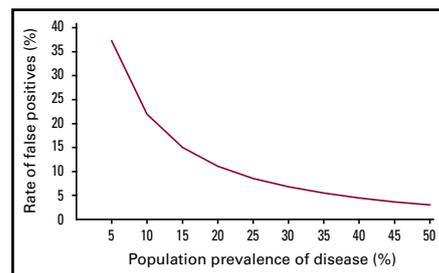


Figure 3. Rate of false positives in a test with 96% sensitivity and 97% specificity

criteria is met [and will not eliminate risk entirely]). If the woman is HSV-1 seronegative, and a sexual partner is HSV-1 seropositive, she should be advised to refrain from receptive oral sex in the third trimester.^{23,24}

Medicolegal aspects of HSV testing

It is important that patients requesting sexual health ‘screening’ and testing for asymptomatic sexually acquired infections not only understand which infections they are having tests for, but also those for which they are not and the reasons why.

Conclusion

In general, HSV serology is not recommended as an STI screening test. Asymptomatic patients requesting HSV serology need to be counselled adequately about HSV, genital herpes and the implications of both a positive and negative result. A sexual history is required to assess their pre-test probability for a positive result. Patients considered low risk for HSV-2 antibodies may potentially have false positive results.

Summary of important points

- Genital herpes presents with self limiting genital lesions, but most people infected are asymptomatic or have unrecognised infection.
- Treatment is not indicated for asymptomatic HSV infection.
- In general, HSV serology is not recommended as a 'screening' test in asymptomatic patients.
- As genital herpes remains a chronic and stigmatised infection, pre-test counselling is important in asymptomatic patients.
- Assessing pre-test probability in asymptomatic patients is necessary. In low prevalence populations there is a higher rate of false positive results.

Conflict of interest: none declared.

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AFP

Correspondence

Email: afp@racgp.org.au