EPIDEMIOLOGY AND TRANSMISSION

Epidemiology

KEY POINTS

- As many as one in five adults have genital herpes due to HSV-2, but most will have asymptomatic or unrecognised disease.
- Genital herpes due to HSV-1 (through oral to genital transmission) has also become common; HSV-1 is a frequent cause of primary genital herpes.
- The natural history of genital HSV-1 infection is towards significantly fewer clinically apparent recurrences and less subclinical shedding than HSV-2.

Genital herpes is an infection caused by the herpes simplex virus (HSV) and, for practical purposes, encompasses lesions on the genitals and nearby areas (i.e. buttocks, anal area and thighs). Genital herpes may be due to HSV-1 (the usual cause of orolabial herpes) or HSV-2 (more commonly associated with genital lesions). It is a very common infection that is often under-recognised, as a person may be asymptomatic or have only very minor symptoms.

HSV-2

HSV-2 prevalence varies between countries, being higher in the USA than in Europe, Australia and New Zealand. It also varies depending on the demographics of the population being tested.[1]1 Consistent findings between countries are that HSV-2 seroprevalence increases with:

Age: The incidence of new infections is highest amongst young adults, but as infection is lifelong, overall prevalence increases with increasing age.[1] Participants in the Dunedin Multidisciplinary Health and Development cohort study provided serum for HSV-2 antibody status at the ages of 21, 26, 32 and 38. By the age of 38, 26.8% of women had been positive for HSV-2 compared to 17.3% for men, confirming a higher biological susceptibility to infection for women. The infection rate for women was highest at age 21-26 compared to 26-32 for men and then declined in both genders with age, consistent with decreasing infectivity of long-term prevalent infections.[2]

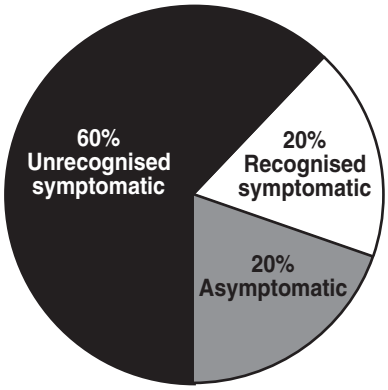

Figure 1: Prevalence, manifestations of genital herpes

HSV-1

HSV-1 seroprevalence studies cannot distinguish between oral and genital infection sites which makes it much more difficult to estimate the prevalence of genital HSV-1 infection. Clinical case data has limitations as well. That said, HSV-1 accounts for 35% of confirmed anogenital infections in Australia[3] and similarly a Waikato-wide study found 30-40% of anogenital isolates are due to HSV-1 each year.[4] In that study, HSV-1 accounted for 53% of positive isolates from under-25 year olds, 30% in the 25-35 year olds, and 26% from over-35 year olds. Likewise, an Auckland Sexual Health Clinic study in 2004 found most true primary episodes of genital herpes were HSV-1, whilst non-primary first episodes and recurrences were mostly HSV-2.[5]

Like HSV-2, HSV-1 seroprevalence increases with increasing age and tends to be more common in women.[6]

Note: Routine typing of isolates enhances a clinician's ability to give prognostic information and optimal clinical care. It is no longer accurate to assume that genital herpes is due to HSV-2 infection, as a substantial proportion of people will have HSV-1.[7] The natural history of genital HSV-1 infection is towards significantly fewer clinically apparent recurrences and much less subclinical shedding.[8,9] Also, prior HSV-1 infection does not alter the risk of acquisition of HSV-2, although it does attenuate the symptoms; it is important for those diagnosed with HSV-1 genital herpes to understand that they remain at risk of HSV-2 infection.

Transmission

KEY POINTS

- Transmission occurs during skin-to-skin contact when virus is being shed.
- HSV-1 is commonly transmitted through oral to genital contact.
- HSV-2 is transmitted through genital to genital contact.
- Virus shedding may be symptomatic or asymptomatic.

Most infections are acquired from someone who is unaware they are infected, who may have mild or asymptomatic infection.

Herpes simplex virus enters the body, either through a break in the skin or through mucous membranes, during direct contact with infected secretions or mucosal surfaces. For genital infections, this is usually during sexual contact, with HSV-2 commonly transmitted during vaginal or anal sex and HSV-1 commonly passed on through oral-genital sex.

Transmission is most likely to occur:

- During sexual contact.
- When the skin is broken.
- When there are lesions (e.g. vesicles or ulcers) present.
- From men to women.

Therefore, sexual contact should be avoided when active lesions are present.

Transmission may occur when a partner is shedding virus asymptomatically. Most people who acquire genital herpes get it from someone who is unaware they are infected, who may have mild or asymptomatic infection.[9]

It is important to remember that not all first episodes of HSV-1 or HSV-2 represent a new or recently acquired infection. It may be a first clinically recognised episode of a previously unrecognised or asymptomatic infection acquired weeks, months or years previously.

The virus is readily inactivated at room temperature and by drying; hence, non-contact forms of spread, for example via fomites (inanimate objects) are considered unlikely. Autoinoculation resulting in spread to different anatomical sites can occur (e.g. orolabial, whitlow), although this is believed to be uncommon. GRADE C

Asymptomatic viral shedding

Nearly everyone, both men and women, with genital HSV-2 infection sheds virus from time-to-time without symptoms, which is why sexual transmission can occur during asymptomatic periods. These intermittent episodes of asymptomatic viral shedding are more frequent:

- With genital HSV-2 than genital HSV-1 infection.
- During the first 12 months after acquiring HSV-2.
- In those with more frequent symptomatic episodes.
- Within a week before or after a symptomatic episode.
- In those with HIV infection.

The viral load threshold for transmission from an episode of asymptomatic shedding has not been established. For a given individual it is impossible to be certain when asymptomatic viral shedding occurs, but it is important not to give the impression that people are infectious all the time.

Reducing risk of transmission

KEY POINTS

- Using condoms reduces, but does not eliminate, the risk of male to female transmission.
- Sexual contact should be avoided when oral or genital lesions are present.
- Aciclovir and valaciclovir suppress symptomatic and asymptomatic shedding by up to 80-95%.
- Prior HSV-1 means HSV-2 infection is more likely to be asymptomatic.
- Suppressive oral antiviral treatment will significantly reduce, but not eliminate, the risk of transmission.

Barrier methods

Male and female latex condoms appear impermeable to HSV-2, but in 'real-life' do not give absolute protection for a variety of reasons: condoms do not cover all affected areas, condom breakage or slippage may occur, close genital contact or contact with infectious secretions may occur during foreplay, etc.[10] Nonetheless, consistent condom use offers moderate protection against HSV-2 infection in both men and women.[11] **GRADE B** Data on male condoms preventing transmission to men or on the efficacy of female condoms is lacking. Condom use should be discussed and left to the individual couple's choice.

Oral-genital contact

People who do not acquire HSV-1 during childhood are at risk of HSV-1 at any site, including genital infection, during adulthood. Transmission may occur whilst receiving oral sex from someone who has oral HSV-1, even if the source partner is asymptomatic. It is estimated that up to a third of persons who are HSV-1 antibody positive do not have a clinical diagnosis of oral herpes,[12] but will still shed HSV-1 virus.[13] It is generally accepted that prior orolabial HSV-1 infection protects an individual against genital HSV-1. Possible exceptions may be those infected simultaneously at more than one site or those with very recent HSV-1 infection who have not yet seroconverted. Oral HSV-2 in isolation is uncommon.

Oral-genital contact should be avoided when oral lesions are present. **GRADE C**

Antivirals

Aciclovir, famciclovir and valaciclovir all suppress symptomatic and asymptomatic shedding, by up to 80-95%.[14] Also, it has been shown that suppressive once-daily valaciclovir results in reduced transmission to the discordant partner.[15] For partners, there was a 48% reduction in acquisition of HSV infection and a 75% reduction in clinical symptomatic genital herpes. Other antivirals may be similarly effective, but this has not been proven in clinical trials.

Co-infection

In most studies, pre-existing HSV-1 infection does not decrease the risk of HSV-2 infection, but prior HSV-1 means HSV-2 infection is more likely to be asymptomatic.[16] If HSV-2 genital infection is acquired first, then a new HSV-1 genital infection does not affect the frequency of recurrences.

Diagnostic tests

KEY POINTS

- Suspected genital herpes should be confirmed by appropriate laboratory tests.
- For patients with active lesions, PCR is the gold standard, or culture (depending on local laboratory availability), but not serology, are the recommended diagnostic methods.
- A negative result does not rule out HSV infection.
- Serology is not recommended as an acute diagnostic tool but may be useful in specific clinical situations (see page 10).

Clinical diagnosis alone is insensitive and inaccurate, with a 20% false positive rate.[16] **Suspected genital herpes must be confirmed by appropriate laboratory tests.** Recurrent lesions, which may be atypical, likewise should be tested for HSV. **However, it is important not to delay appropriate therapy while awaiting confirmation.**

Detection of herpes simplex virus in the lesion establishes the diagnosis. Viral detection may involve culture or HSV DNA. Vesicles offer the best source of virus. However, results depend on multiple factors, including the adequacy of the specimen, and a negative result may not exclude infection. If direct HSV tests are repeatedly negative and the symptoms are recurring, the patient should be advised to have type-specific herpes serology. GRADE B

PCR

For patients with active lesions, PCR is the recommended diagnostic method.

HSV DNA detection by polymerase chain reaction (PCR) increases HSV detection rates compared with virus culture. This is largely because it avoids problems that may affect culture results, such as inadequate quantity of specimen, bacterial contamination and inadvertent inactivation of virus by sub-optimal handling and sample transport delays. Increasingly, PCR is being implemented as the preferred diagnostic method for genital herpes, particularly since the advent of commercially available real-time assays.

The sensitivity of HSV2 on a commercial PCR system has been demonstrated to be 98.4%-100% sensitive and with a specificity of 87% compared to an in-house PCR. For HSV-1 the sensitivity and specificity have been estimated at 96.7-100% and 95.1-99.4%.[17]

However, stringent quality control is necessary because of potential contamination by 'carryover' DNA from other biological samples[18] and local validation is recommended. Positive results are usually reported within 2 days but occasionally take longer.

Culture

HSV isolation in cell culture has been the diagnostic gold standard for many years. Specificity of culture is virtually 100%, but sensitivity is highly dependent on the stage of the clinical lesions, with an isolation rate of over 90% from vesicular or pustular lesions, 70% from ulcerative lesions, but only 27% at the crusting stage.[19] Delayed transport of the specimen to the laboratory may further reduce yield. Positive results are usually reported within 2-5 days, but occasionally may take longer.

Sample collection

The following tests have a low false positive rate. However, a negative test result does not necessarily exclude HSV infection since all methods are dependent on adequate collection of the specimen and, for culture in particular, on correct specimen handling and prompt transportation to the laboratory. It is important to be aware of locally available tests, as these may vary, so an appropriate sample is taken. If there is doubt please check with your local laboratory.

Viral typing should be requested routinely.

PCR

- PCR is the test of choice
- Check with local laboratory if HSV PCR is routinely available. If not, you may need to specify "for herpes simplex DNA" and offer clinical explanation as to why this is the preferred test over culture, e.g. CSF sample.
- Swab as for viral culture.
- Transport time to the laboratory is less important than with culture.

Culture

- Select appropriate viral transport swab (check with local lab as to which swab to use).
- Swab the lesion firmly. The aim is to collect any vesicular fluid that may be present and to collect virus-infected cells from the base of the lesion.
- Insert swab into plastic tube.
- Place on a cold source, e.g. melting ice or slikka pad, and send chilled to the virus laboratory. The swab should arrive the same day since the virus will decay with transport time.

Serology

Serology is not recommended as a routine test for the following reasons:

- Serological tests detect antibodies to HSV in blood and indicate **past** infection.
- Type specific tests, based on glycoprotein G (gG) assays, detect antibodies to the type specific proteins gG-1 and gG-2 and detect established infection with HSV-1 and HSV-2. They do not distinguish the anatomical site of infection (see Table 1 on page 11).
- Type specific tests are used in population surveys, but their diagnostic reliability in individual patients is still debated.
- **There is no confirmatory serology testing available in New Zealand.**
- Seroconversion following initial infection is usually 2-6 weeks, but may be longer (months). Also, some do not seroconvert and reversal from seropositive to seronegative status may occur if there is minimal antigenic stimulation.
- It is a useful test in some clinical situations, but routine screening of asymptomatic individuals is currently not recommended. GRADE B

Situations where measurement of type-specific antibody might be helpful include:

- Management of herpes in pregnancy (see page 27).
- Where one partner in a relationship has symptomatic genital herpes. This may be important for discordant couples (a pregnant woman with a symptomatic male partner), as it may be appropriate to counsel abstinence in the last weeks of pregnancy and/or for the male partner to take suppressive antiviral therapy.
- Recurrent or atypical genital symptoms with negative HSV cultures and/or PCR. Most recurrences will be positive on PCR testing and may not require serology to be done
- For most partners of positive patients, education and not serology is recommended because of false positive/false negative serology results.

With the widespread introduction of PCR, which detects most HSV recurrences, the need for serology has decreased.

The person ordering serology should be able to supply appropriate pre- and post-test counselling. A positive HSV-2 serology result may cause significant psychological morbidity (see page 15-16).

KEY INFORMATION TO DISCUSS WITH A PATIENT WHO ASKS FOR A BLOOD TEST

- Explain whether the test is for HSV-1 and HSV-2 antibodies or just HSV-2 antibodies. If the blood test being done only tests for HSV-2 antibodies, a negative test does not rule out the possibility of the person having genital herpes caused by type 1.
- The window period for antibodies developing following infection is usually 2-6 weeks, but may be longer (months).
- Caution is needed in the interpretation of results. Because false negatives and false positives occur, the results have to be weighed together with the clinical presentation and patient's history.
- Implications for the presence of only HSV-1 antibodies need to be explained. HSV-1 is a common infection, usually acquired in childhood, and may be shed from the oropharynx by asymptomatic individuals. Infection with HSV-1 does not necessarily imply sexual exposure, but genital infection with HSV-1 is increasingly common.

Table 1: Interpreting blood test results

	HSV-2 negative	**HSV-2 positive**
HSV-1 negative	No antibodies detected*; consider at risk of infection to both types.	No HSV-1 antibodies detected*; consider at risk of infection to HSV-1. HSV-2 antibodies imply prior infection. Probable genital HSV-2 infection because oral and other non-genital site infections are uncommon.
HSV-1 positive	HSV-1 antibodies imply prior infection, but does not specify site of infection. No HSV-2 antibodies detected*; consider at risk of infection to HSV-2.	HSV-1 and HSV-2 antibodies imply prior infection with both. Probable genital HSV-2 infection, and oral HSV-1.

* May be within window period, may not have seroconverted or may have seroreverted.