PART 2J

Genital herpes

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Genital herpes (GH) is the fourth most common sexually transmitted infection diagnosed at genitourinary medicine (GUM) clinics in the United Kingdom.[1] There are two herpes simplex virus (HSV) types; HSV-2 is almost entirely associated with genital disease whereas HSV-1 is associated with both oropharyngeal and genital disease. In some,[2–7] although not all,[8] areas of the United Kingdom HSV-1 accounts for more than 50% of first episodes of GH. Differentiating between HSV types yields important prognostic information. Genital infection with HSV-1 shows a milder natural history than infection with HSV-2 and both symptomatic recurrences and subclinical shedding are less frequent.[9–16]

GH is classified as primary when an HSV seronegative person acquires HSV-1 or HSV-2; initial non-primary when a person with antibody against one virus type acquires the opposite type; and recurrent. Primary and initial infections are often asymptomatic or unrecognised, but can become symptomatic at any time.[9 12 14] Thus a first episode of GH may represent a recently acquired or a long lasting infection. Most asymptomatic individuals with HSV-2 subsequently develop symptomatic disease.[14]

GH is a lifelong infection that can cause substantial morbidity to those infected and have serious consequences, including neonatal herpes and increased risk for HIV acquisition and transmission.[17] As clinical signs and symptoms are often subtle, most infections are unrecognised and undiagnosed.[18 19] Infected people shed the virus intermittently, regardless of whether lesions are clinically apparent.[15]

RECOMMENDED TESTS

Screening of asymptomatic GUM clinic attendees by either HSV antibody testing (evidence level IV, recommendation grade C)[20–24] or HSV detection in genital specimens (evidence level IIa, recommendation grade B)[18 20] is not recommended at present, although this area is under active review.

HSV antibody testing

Testing for HSV type specific antibodies can be used to diagnose HSV infection in asymptomatic people.[18 20]

HSV-2 antibodies are indicative of GH. HSV-1 antibodies do not differentiate between genital and oropharyngeal infection.[18]

Arguments in favour of serological screening include:

- HSV-2 infection rates are as high as or higher than those of other STIs for which screening is in place.[18 25]
- People with asymptomatic or undiagnosed infection may transmit HSV to sexual partners or neonates.[20 26 27]
- Behavioural changes, condom use, and suppressive antiviral therapy reduce the risk of HSV transmission.[28–30]
- Vaccines may soon become available to protect HSV seronegative people from infection and disease.[31]
- HSV-2 seropositive people who engage in high risk sexual behaviour can be counselled about the increased risk of HIV acquisition (evidence level Ia, recommendation grade A).[17]

Arguments against screening include:

- The specificity and sensitivity of current antibody assays are <100%.[32 33]
- False positive results generate unnecessary psychological morbidity.
- False positive and false negative results lead to inappropriate counselling.
- Counselling of HSV-2 seronegative HSV-1 seropositive people is problematic, given the large proportion of GH caused by HSV-1.[2–7]

Assays should be used that detect antibodies against the antigenically unique glycoproteins gG1 and gG2 (evidence level III, recommendation grade B).[18 32 33]

- Western blot (WB) is the diagnostic gold standard. It is more than 97% sensitive and more than 98% specific, but is labour intensive and not commercially available.[18]
- Several commercial assays have become available.[33 34] Well validated in-house assays have also been developed.[35] Among commercial assays, the HerpeSelect-1 and HerpeSelect-2 ELISA IgG, and HerpeSelect 1 and 2 Immunoblot IgG (Focus Technology, CA, USA) have been approved by the American Federal Drug Administration. In sexually active adults, sensitivity and specificity of enzyme linked immunosorbent assay (ELISA) relative to WB are 91% and 92% for HSV-1 and 96% and 97% for HSV-2, respectively. Immunoblot sensitivity and specificity are 99% and 95% for HSV-1 and 97% and 98% for HSV-2, respectively.[36]
- HSV seroprevalence rates in the local population and the presence or absence of risk factors for GH influence the positive predictive value of HSV type specific antibody assays. Local epidemiological data and patient demographic characteristics should guide testing and result interpretation (evidence level III, recommendation grade B).[24 32]
- In patients with a low likelihood of GH, a positive HSV-2 result should be confirmed in a repeat sample or by using a different assay (evidence level III, recommendation grade B).[32]
- Type specific antibody can take months to develop and false negative results may occur early after infection.[32] In first episode disease the diagnostic use of type specific antibody testing will require follow up samples after 3 months to demonstrate seroconversion.

Direct detection of HSV in genital lesions

Methods should be used that directly demonstrate HSV in swabs or scrapings from a lesion (evidence level Ia, recommendation grade A).[20 37 38]

Abbreviations: EIA, enzyme immunoassay; ELISA, enzyme linked immunosorbent assay; GH, genital herpes; GUM, genitourinary medicine; HSV, herpes simplex virus; IFA, immunofluorescence assay; PCR, polymerase chain reaction; WB, western blot

Cytological examination (Tzanck and Papanicolaou smears) has modest diagnostic specificity and sensitivity and should not be relied upon for diagnosis (evidence level Ib, recommendation grade A).[9 38]

HSV isolation in cell culture is the diagnostic gold standard and the current routine diagnostic method in the United Kingdom.[39] Isolates can be typed and tested for antiviral susceptibility. Virus culture is slow, labour intensive, and expensive. Specificity is virtually 100%, but levels of virus shedding, quality of specimens, and transport conditions influence sensitivity.[9 40–42] First episode ulcers more often yield the virus than recurrent lesions (82% versus 43%).[9] Average sensitivity is 52–93% for vesicles, 41–72% for ulcers, and 19–27% for crusted lesions.[9 40] Delayed sample processing and lack of specimen refrigeration after collection and during transport significantly reduce the yield of virus culture.[41]

HSV DNA detection by polymerase chain reaction (PCR) increases HSV detection rates by 11–71% compared with virus culture.[37 40–48] HSV PCR is widely available in UK virology laboratories for testing of cerebrospinal fluid in patients with neurological disease.[39] There have been at least 14 large studies comparing virus culture with PCR for the detection of HSV in mucocutaneous swabs, together comprising data from over 3500 patients. These studies demonstrated that the relative sensitivity of virus culture averaged 70% and ranged between 25% and 89%. PCR should be implemented, after local validation, as the preferred diagnostic method for GH (evidence level Ib, recommendation grade A).[37 40–48]

Unlike virus culture, PCR based methods do not rely on virus growth and may allow less stringent conditions for sample storage and transport.

Real time PCR assays allow detection and typing of HSV in a single reaction tube, with faster turn around times (potentially 2 hours) and lower risk of contamination than traditional PCR assays.[42] The RealArt HSV 1/2 PCR kit (Artus, Germany) is commercially available for use in real time assays.

Viral antigen can be detected by direct immunofluorescence assay (IFA) using fluorescein labelled monoclonal antibodies on smears, or by enzyme immunoassay (EIA) on swabs.

IFA shows lower sensitivity (74%) and specificity (85%) than virus culture and cannot be recommended (evidence level Ia, recommendation grade A).[49]

Commercially available EIAs (for example, HerpChek, PerkinElmer, Belgium) show ⩾95% specificity and 62–100% sensitivity relative to virus culture.[43–45 50–54] Sensitivity may be higher than virus culture for typical presentations and late specimens, but lower for cervical or urethral swabs and recurrent episodes.[43–45 50–54] HerpChek does not differentiate between HSV types.

RECOMMENDED SITES FOR TESTING

- Clotted blood (if serology indicated)
- Lesion material (if lesion is present).

FACTORS THAT ALTER TESTS RECOMMENDED OR SITES TESTED

- Genital lesions that could be caused by HSV (direct detection)
- Serological screening should be considered in people with a history of recurrent genital symptoms of unknown aetiology when direct virus detection methods (virus culture or PCR testing of genital specimens) have been repeatedly negative (evidence level III, recommendation grade B).[18 21–24]
- Patients who are known contacts: serological screening should be considered for sexual partners of people with GH, where there is a concern about transmission. Some couples may find that their HSV status is concordant. Discordant couples can identify strategies to prevent transmission (evidence level III, recommendation grade B).[20–24 32]

Risk groups

- Homosexual men: no alteration to standard recommendation
- Sex workers: no alteration to standard recommendation
- Young patients: HSV-2 antibody tests should not be used in children <14 years of age because of a high false positive rate (evidence level III, recommendation grade B).[32]

Other groups

- Pregnant women: routine screening of pregnant women, and their partners, to identify those already infected and those at risk of infection remains controversial.[55] The identification of serologically discordant couples may offer the opportunity to counsel seronegative women about strategies to prevent infection during pregnancy (evidence level III, recommendation grade B).[20 21 56–58] Screening of pregnant women is recommended where there is a history of genital herpes in the partner (evidence level III, recommendation grade B).[56–58]
- Women with a history of hysterectomy: no alteration to standard recommendation.

RECOMMENDATION FOR FREQUENCY OF REPEAT TESTING

- In people with a low likelihood of infection, a positive HSV-2 antibody result should be confirmed in a repeat sample or by using a different assay.
- Repeat testing of HSV seronegative women with seropositive male partners may be helpful in pregnancy.
- The decision about repeat testing should be guided by the patient's history of potential exposure.
- In patients with a suspected recent infection who test HSV antibody negative early after presentation, repeat serological testing is recommended after 3 months as seroconversion may be delayed.[32]
- Repeat direct testing for HSV in genital specimens is not indicated in the presence of typical recurrent HSV lesions as long as viral detection and typing were successfully accomplished during a previous episode.

RECOMMENDATION FOR A TEST OF CURE

Not recommended.

STAKEHOLDER INVOLVEMENT

BASHH Herpes Special Interest Group (at time of writing): Dr Simon Barton, Dr David Brown, Dr Frances Cowen, Dr Susan Drake, Dr Anna Maria Geretti, Dr John Green, Dr James Hickling, Dr George Kinghorn, Dr Patricia Munday, Ms Marian Nicholson, Dr Raj Patel, Dr Anne Scoular, Dr Derek Timmins, Dr Mark Whitaker, Dr Paul Woolley.

RIGOUR OF DEVELOPMENT

MeSH: ''Herpes-genitalis-diagnosis,'' ''Herpes-simplex-diagnosis,'' ''Sensitivity,'' ''Specificity'' (1983 to April 2004). Further evidence was obtained from the International

Herpes Management Forum guidelines[59] and the 2002 Center for Disease Control STI treatment guidelines.[60]

APPLICABILITY

HSV type specific antibody assays may not be available in all laboratories.

AUDITABLE OUTCOME MEASURES

- HSV antibody tests that do not discriminate between virus types should not be used for the diagnosis of GH. Target 100%
- In HSV-2 seropositive people with a low likelihood of infection, a positive HSV-2 result should be confirmed in a repeat sample or by using a different assay. Target 100%.

Conflict of interest: The Herpes Special Interest Group is a special interest group of the MSSVD, currently sponsored by an educational grant from GlaxoSmithKline. Members have undertaken research and been funded to attend meetings by GlaxoSmithKline

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Before submission this guideline was distributed to all members of the Herpes Special Interest Group. Their comments were noted and incorporated into the current document.

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