Clinical Guidelines from the Swedish Section of Venereology

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The Swedish Section of Venereology has previously presented clinical guidelines for anogenital Chlamydia trachomatis infection, including lymphogranuloma venereum, Mycoplasma genitalium infection and gonorrhoea in Forum for Nord Derm Ven (2009, Vol. 14, No. 4, p. 101–103; 2010, Vol. 15, No. 2, p. 36–37; 2010, Vol. 15, No. 3, p. 68–70, respectively). In this issue we extend this information with an update on genital herpes infections. In later issues we will address syphilis, ulcus molle, non-specific urethritis and cervicitis, trichomoniasis and genital papillomavirus infection.

Genital Herpes Simplex Virus Infection: Clinical Guidelines from the Swedish Section of Venereology

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Background and clinical features

Genital herpes is one of the most common sexually transmitted infections in the world. The infection can cause both physical and psychological problems for a patient. Furthermore, genital herpes simplex virus (HSV) infection increases the risk of HIV transmission.

Genital herpes can be caused by HSV type 1 (HSV-1) or type 2 (HSV-2). The typical presentation is that of vesicles and ulcers surrounded by an erythema. It is not possible to distinguish between HSV-1 and HSV-2 infection based on the clinical picture alone, but a diagnosis can be made by polymerase chain reaction (PCR) technique, viral isolation or seroconversion. HSV-2 is the main cause of recurrent genital lesions, while HSV-1 has been shown to be a common cause of primary genital infection, especially in women. However, most patients with HSV infections are either truly asymptomatic or unaware of their infection. Studies have shown that many patients can be taught to recognize their genital infection, showing that they have had unrecognized symptoms.

The incubation period for primary genital HSV infection is 2–20 days (mean 6 days) and the infection can present itself with bilateral, painful genital vesicles, pustules or ulcers and dysuria. Systemic symptoms, such as fever, lymphadenopathy and myalgia, are common. Urinary retention can also occur. A primary infection may last up to 3 weeks. The clinical manifestations of recurrent HSV infections are significantly milder, with unilateral genital vesicles or ulcers, and the symptoms often resolve within 1 week. Lesions can also be localized on the buttocks or perianally and appear as fissures. Atypical HSV infection can be misinterpreted as, for example, recurrent urinary tract infection or *Candida* vulvovaginitis. Almost half of the patients experience prodromal symptoms, starting a couple of hours up to 2 days before visible signs of a lesion appear.

HSV is transmitted through sexual contact, including oral sex. Unrecognized infections and asymptomatic viral shedding are major factors in the viral transmission of HSV.

Laboratory diagnosis

Indications for testing
Genital vesicles, pustules or ulcers.
Recurrent, atypical genital symptoms.

Testing should be performed in primary HSV infection, as well as in patients with undiagnosed recurrent genital HSV infection. Viral typing is of importance, and information about the result should be conveyed to the patient, since recurrences are

much less common in genital HSV-1, compared with genital HSV-2 infection.

In patients with a history of sexual contacts in settings where syphilis or chancroid is prevalent, testing for *Treponema pallidum* and *Haemophilus ducreyi* should also be performed. In men who have sex with men (MSM) it is also important to consider syphilis and lymhogranuloma venereum, if genital ulcers are present. HIV testing should be offered.

For viral detection PCR should be used and PCR testing is now performed in most laboratories. This method has a sensitivity 15–30% greater than the sensitivity of viral isolation.

In most laboratories type-specific HSV-serology, based on glycoproteins G-1 and G-2, is available. These serological tests discriminate between HSV-1 and HSV-2 antibodies.

In untreated primary infection the period of HSV shedding is 7–12 days (data based on viral isolation), while viral shedding during untreated recurrences is seen during 1–4 days (data based on viral isolation).

PCR: Material from blisters or eroded lesions is collected with a sterile cotton-tipped swab. The swab is transported in a tube with NaCl or specific transport medium.

Viral isolation is used almost exclusively for resistance testing. Testing is performed as for PCR.

Type-specific HSV-2 serology is not used routinely, but can be performed in couples where one partner has symptomatic genital HSV infection and the other does not, e.g. a male with genital HSV infection and a pregnant partner without known HSV infection. It can also be of value in patients presenting with recurrent, atypical genital symptoms or before starting suppressive therapy in patients where the infection has not been verified with HSV-2 PCR.

Treatment

Antiviral therapy has been shown to decrease viral shedding and symptoms associated with the disease. This treatment has been accessible since the 1980s and development of resistance is uncommon. However, in immunosuppressed patients the risk of developing resistance to antiviral therapy is increased from < 0.5% in immunocompetent subjects to 5% among immunocompromised patients. Resistance is mostly conferred by mutations in the virus-encoded thymidine kinase gene, which results in inactivation of the antiviral drug. In resistant HSV infections higher doses and longer periods of antiviral treatment can be tried, but if this proves ineffective, treatment with intravenous foscarnet can be employed. Local antiviral treatment has no place in the treatment of genital herpes at present.

Primary genital herpes infection
Treatment significantly reduces the symptoms and shortens the period of primary infection. It is indicated to start treatment as long as new lesions develop. Peroral treatment with aciclovir 200 mg × 5, or 400 mg × 3, valaciclovir 500 mg × 2, or famciclovir 250 mg × 3 can be given for 5–10 days. If needed, give local or peroral analgesics. Occasional patients may need admission to hospital and intravenous aciclovir treatment.

Recurrent genital herpes infection
Episodic treatment for recurrences is not always needed, but if used, it should be started early during a recurrence in order to be effective (patient-initiated therapy). Aciclovir 200 mg × 5 or 400 mg × 3, valaciclovir 500 mg × 2 or famciclovir 250 mg × 2 for a period of 3 days can be recommended. Data show promising effect also for shorter courses, i.e. single-day treatment with higher doses of the antiviral drug.

Suppressive antiviral therapy
Daily suppressive therapy is indicated in frequently recurring disease, defined as ≥ 6 recurrences a year or in patients with lengthy or complicated recurrences. Aciclovir 400 mg × 2, valaciclovir 500 mg × 1 or 250 mg × 2 can be employed. In patients with ≥ 10 recurrences per year, treatment given twice daily is preferable. In spite of daily treatment occasional recurrences can occur and doses can then be increased to aciclovir 400 mg × 3 or valaciclovir 500 mg × 2 for 3 days.

After 4–6 months a treatment interruption should be made in order to evaluate the need for further suppressive therapy. Suppressive therapy reduces viral shedding, but the risk for sexual transmission of HSV does not disappear completely.

Antiviral therapy in pregnancy
For Swedish guidelines, see www.lakemedelsverket.se or www.infpreg.com.

Special considerations
Allergic reactions to aciclovir, valaciclovir or famciclovir are very rare. If there is a strong need for antiviral medication foscarnet can be considered. Desensitization to aciclovir has been described.

Follow-up
Providing information to the patient about genital herpes infection, recurrences, treatment and viral transmission is of great importance. Condom use reduces, but does not eliminate, the risk of transmission of HSV.

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Comments on the Guidelines – Edited by Tomas Norman Dam

Specific comments on these guidelines were given by Bolli Bjarnason, Carsten Sand, Harald Moi, Bernt Lindelöf, Robert Gniadecki, Sari Suomela and Eija Hiltunen. The comments have been compiled into a summary here, edited and commented on further by Continuous Medical Education (CME) editor Tomas Norman Dam. Forum readers are invited to e-mail any further comments on the guidelines to cme@medicaljournals.se, and these will be presented for open discussion in the CME section in the next issue.

General comments and comments on the recommended treatments

The recommendations set out in the guidelines are in good agreement with Danish, Finnish and Icelandic recommendations and with the International Union against Sexually Transmitted Infections (IUSTI) European guidelines used in Norway. There was agreement among all editors that "These guidelines would serve the same purpose in their country with regard to specific regulations, etc." It was specifically commented that, "Otherwise healthy patients with frequent recurrent genital herpes may need higher doses of either oral valaciclovir (500 mg or 1 g twice daily) or famciclovir 500 mg × 1–3 times daily to suppress recurrences" (Carsten Sand). According to the Finnish guidelines, recurrent infection is treated with (low-dose) famciclovir 125 mg × twice daily for 5 days (Sari Suomela).

Comments on the diagnostic approach

In Finland polymerase chain reaction (PCR) is not available everywhere and culturing is widely used for diagnosis. For screening a method based on gene amplification from urine samples is routinely used, while culture samples are taken only if patients have symptoms. More specifically, it was recommended that laboratory processing of the transport medium for culture should be carried out on the same day, because decreased sensitivity has been observed if processing is delayed until the next day.