



## Genital Herpes Current Perspectives

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### Abstract

Herpes Simplex Virus-2(HSV-2) is a leading cause of vulvar ulcer disease. It is a sexually transmitted infection with recurring manifestations throughout the lifetime of infected patients. Primary and recurrent infections result in lesions on the genital area. Immuno compromised patients are susceptible to additional systemic infections including chronic non-healing ulcers. Currently prescribed medications, mostly nucleoside analogs, only reduce the symptoms caused by an active infection, but do not eliminate the virus. Adequate clinical and laboratory diagnosis as well as effective treatment is the best clinical approach to treat this recurrent disease.

Genital herpes is one of the most common, persistent and highly infectious sexually transmitted viral infection caused by HSV 1 or HSV 2. Chronic herpetic genital ulcerations have become more prevalent since the start of the HIV epidemic and the relationship between these two viruses is increasingly important. Recurrent vulvar ulceration is usually caused by Herpes Simplex Virus (HSV) type 2. Differential diagnosis in patients with chronic vulvar ulcerations includes erosive lichen planus, lichen sclerosis, mucous membrane pemphigoid, pemphigus and Behcet's disease<sup>[1]</sup>. This review aims to optimize the diagnosis, treatment and prevention of this challenging clinical condition.

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### Introduction

Genital ulcer may be caused by infectious and non-infectious etiologies<sup>[2]</sup>. Sexually transmitted infections that generate genital ulcers include Herpes Simplex Virus (HSV), chancroid (*Haemophilus ducreyi*), syphilis (*Treponema pallidum*), and granuloma inguinale (*Calymmatobacterium granulomatis*) and lymphogranuloma venereum (*Chlamydia tracomatis*). Other non-sexually transmitted infections and fungi can also cause genital ulcers. Genital herpes is a common, persistent and highly infectious sexually transmitted viral infection most commonly caused by Herpes Virus Type 2 (HSV-2) .

### Epidemiology

The global incidence of genital ulcerative disease is over 20 million cases per year<sup>[3]</sup> Worldwide, more than 400 mil-

lion persons are infected with genital herpes caused by HSV-2<sup>[2]</sup>. In the United States approximately 20% of reproductive age women have been exposed to HSV type 2 viruses<sup>[4,5]</sup>. Genital herpes is predominantly transmitted by sexual contact. HSV-2 seroprevalence rates varies among the community, being above the levels of the general population in patients engaging in high risk sexual behavior and in individuals living with HIV.

During the past few decades, the prevalence of HSV-1 has decreased, particularly among children<sup>[6]</sup> Therefore, there is a higher proportion of primary genital herpes caused by HSV-2 infections and a higher proportion of genital disease caused by HSV-1 acquired through oral sex among adolescents and adults. However, HSV-1 is less likely to lead to recurrences in the genital tract than HSV-2<sup>[7]</sup>.



### Pathophysiology

Genital herpes infection results from sexual contact of a previously unexposed individual with a partner who is actively shedding the virus. The contact is followed by a prodromethat could last from hours to several days consisting of pain, itching, burning or tingling at the site of infection. There is epithelial skin damage that leads to eruption of vesicles that subsequently rupture, ulcerate, and re-epithelialize that if left untreated, the lesions last about 10 to 14 days. During the initial infection, viral DNA enters the central nervous system and travels by the axon to the spinal cord sensory ganglion where it persists for life.

### Infectious causes of genital ulcerative disease

#### Clinical symptoms

Genital herpes is predominantly transmitted through sexual contact. Viral transmission by oral-genital contact is also frequent. Virus shedding is predominant in mucosal surfaces like mouth and vagina. Direct contact with an infected surface increases the risk of acquiring HSV.

When the patient encounters HSV for the first time the initial symptoms may occur anywhere between 2 days to 2 weeks after primary infection. Primary infections are clinically most severe and most likely symptomatic<sup>[8,9]</sup>. Systemic symptoms like fever, itching and muscle pains are common in primary infection; other frequently reported symptoms include fever, headache, and general malaise. Papule formation followed by blisters appears on the genital areas that eventually break to form painful ulcers. (Figure-1, 2)



**Figure 1:**



**Figure 2:**

Primary infections either by HSV-1 or by HSV-2 are clinically identical. At the tissue level, HSV-2 infects the epithelial cells on the genital mucosa leading to an increase in inflammatory response. This contributes to a chronic inflammatory state of the genital skin and mucosa which play an important role in cases of chronic ulceration. During the primary infection, the virus spreads to the Dorsal Root Ganglia (DRG) where it remains latent. Upon reactivation, the virus spreads from the DRG to the epithelial cells where replication of the virus follows, resulting in virus shedding. The severity of viral reactivation varies widely from person to person and depends on cell mediated immunity that is considered important for control of viral replication<sup>[9-12]</sup>.

### Laboratory diagnosis

#### Virus detection

HSV-1 and HSV-2 can be detected in skin lesions in patients with acute genital herpes Infections or in the absence of active lesions from normal areas of genital mucous membranes to confirm asymptomatic viral shedding. In the presence of active lesions, swabbing the lesions is the collection of method of choice. Acute genital HSV infections are diagnosed by detection of DNA of HSV-1 and HSV-2 by means of Polymerase Chain Reaction (PCR). Also, acute genital HSV infection or asymptomatic shedding can be diagnosed by viral isolation in cell culture. In general, the viral culture has been accepted as a sensitive method for detection of HSV, since both HSV-1 and HSV-2 replicate well. However, because of the higher sensitivity, the PCR technique is currently accepted as gold standard. It is important to note that laboratory methods, which diagnose HSV-1 or HSV-2infection by viral growth, detection of DNA, or viral antigens, do not distinguish between primary HSV infection, recurrent HSV infections, and HSV shedding.

#### Determination of antibodies

HSV serological methods are used for the diagnosis of infections caused by HSV-1 or HSV-2. Serological methods are

especially important for the diagnosis of primary HSV infection when seroconversion of virus-specific IgG antibodies can be observed. The detection of IgG seroconversion can also be performed using HSV type-specific antibody assays.

If serum sample from the early phase of disease is available, the detection of HSV-1 and HSV-2 DNA using type-specific PCR in combination with the type-specific detection may permit a distinction between primary and recurrent infections. For example, when HSV-2 is detected in genital lesions, primary herpes can be distinguished from recurrent genital herpes using type-specific HSV serology. A negative anti-HSV-1 or anti-HSV-2 IgG excludes recurrent HSV-1 or HSV-2 infections<sup>[13]</sup>.

### Diagnosis

The presence of multiple painful small vesicular or ulcerated lesions in the genital area strongly suggests genital herpes. Laboratory confirmation of the clinical diagnosis is strongly recommended. A definitive diagnosis is warranted given the complex social and psychosexual implications of genital herpes. Moreover, an incorrect clinical diagnosis without laboratory confirmation may lead to years of unneeded antiviral therapy. Finally, in some clinical situation such as women who may become pregnant; a diagnosis of genital herpes could have serious implications if left untreated. Detection of HSV-2-specific IgG is indicative of genital herpes, even in patients who do not have a clinical history of the infection. The presence of HSV-1 specific IgG is consistent with either genital or non genital infection.

Serologic testing is particularly useful when a patient has a history that suggests recurrent genital symptoms but does not have an active lesion that is suitable to virology testing. If one person in a couple is known to have genital herpes, serologic testing can provide information useful in counseling regarding risks of transmission.

### Treatment

Acyclovir, valacyclovir, and famciclovir are effective therapies for genital herpes caused by HSV-1 or HSV-2. These antiviral have an excellent safety profile and the efficacy is generally similar, drug selection is based on clinician and patient preference, and cost of the medication. Intravenous acyclovir should be used when the manifestations of genital herpes are especially severe or are accompanied by complications, particularly in immune compromised patients. Topical antiviral therapy for genital herpes is less effective than systemic therapy and is not recommended.

Primary genital HSV infections associated with more severe symptoms and warrants treatment. The most convenient regimen is valacyclovir 1 g orally twice daily for 7 to 10 days. Analgesics and site baths will decrease local pain. Other options with similar efficacy include the use of acyclovir and fancyclovir.

Patients with symptomatic recurrences of genital herpes can receive episodic or suppressive therapy. Both episodic and suppressive therapies result in clinically significant improvements in perceived quality of life<sup>[14]</sup>. An additional benefit of suppressive therapy is that it also significantly reduces the frequency of asymptomatic shedding of HSV-2. This reduction in frequency of shedding reduces the risk of transmission among discordant couples. Suppressive therapy should be offered to all patients who have genital herpes, even those who have relatively

infrequent symptomatic recurrences. The most convenient suppressive regimen is valacyclovir at a dose of 1000 mg orally once daily. Long-term suppressive therapy is almost never associated with the development of acyclovir-resistant virus in immune competent patients. (Figures-3, 4, 5)



Figure 3:



Figure 4:



**Figure 5:**

**Prevention**

Patients with history of HSV should be encouraged to disclose their history of genital herpes to their sex partner. Patients with active lesions should abstain from sexual activity until lesions have completely healed. The use of condoms among discordant couples should be strongly recommended. Condoms are more effective in preventing HSV transmission from men to women than from women to men.

**Table 1:** Infectious causes of genital ulcerative disease.

Etiology	Sign and Symptoms	Diagnosis	Treatment
HSV-1 or HSV-2	Multiple painful vesicles that rupture	HSV culture or PCR testing from ulcer	Acyclovir Fancyclovir Valacyclovir
Syphilis	Single, painless ulcer with clean base and well demarcated indurated borders	Positive serologic nontreponemal testing confirmed (VDRL or RPR) confirmed by a positive treponemal testing (FTAs)	Penicillin G benzathine
Chancroid	Non-indurated painful ulcer with irregular borders and friable base	H Ducreyi identified in culture	Azithromycin
Lymphogranuloma venereum	Shallow, painless small papule or ulcer. Tender lymphadenopathy	Positive Chlamydia trachomatis type L1, L2 or L3 culture	Doxycycline
Granuloma Inguinale	Persistent, painless, highly vascularized papules or ulcers	Intracytoplasmatic Donovan bodies on Wright stain	Doxycycline Azithromycin Ciprofloxacin Erytromycin

Trimethopin/Sulfametoxazole

**Conclusion**

Genital herpes is a common sexually transmitted infection that affects mostly individuals of reproductive age. The medical management of affected patients is often frustrating to the patient, their partners and the physician involved in their care. Considering the present possibilities of laboratory diagnosis, antiviral therapy, and prevention by suppressive antiviral treatment, the management of patient’s including their counseling may significantly be improved.

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