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Genital Herpes

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Abstract

Genital herpes is a chronic, nearly always active herpes simplex virus (HSV) infection of sacral ganglia, that may appear bilaterally and in more ganglia than previously thought. It represents one of the most prevalent sexually transmitted infections, and the most frequent cause of genital ulcer disease in the general populations of developed countries. It is caused by HSV type-2 (HSV-2) in 60-80% of cases, with HSV-1 infections causing the remainder. Genital herpes caused by HSV-1 is on the rise. Since genital HSV-1 infections have higher risk for transmission from mother to infant during delivery than HSV-2, they account for 30% of all cases of neonatal herpes. Serological studies have found prevalence of HSV-2 in the general population of developed contries to be up to 25%. Thirty years ago, herpes was defined as "Today's Scarlet Letter" in the absence of reliable serological tests and highly effective medications, for diagnosis and treatment of genital herpes. In 2000, apart from virus isolation in cell culture (70% sensitivity), that has long been regarded as the diagnostic gold standard, type specific serological tests and higly effective antiviral agents have evolved. However, the following questions were raised: should serological testing be routinely recommended in asymptomatic patients; can antiviral therapy reduce asymptomatic shedding of the virus; can antiviral therapy reduce sexual transmission of infection; can antiviral therapy reduce acquisitation of viral copathogens, such as human immunodeficiency virus (HIV)? Now, ten years later, we know the answers. Type specific HSV DNA detection by real-time PCR assays (100% sensitivity) are tests of choice for every person with recurrent genital ulcers lasting more than 4 days, and must be available in those laboratories currently performing a significant number of PCR tests for different purposes. Type specific IgG serology assays are indicated in all asymptomatic persons who are at increased risk for HSV infection. In sexually active patients experiencing ≥ 6 recurrences per year, daily supressive dose of acyclovir, valacyclovir or famciclovir should be discontinued after a maximum of a year of continuous antiviral therapy in order to reassess recurrence frequency. If necessary, the therapy should be restarted after at least two recurrences. With such expansive diagnostic possibilities and more aggressive therapeutic approaches, we can define genital herpes not as a "Scarlet Letter", but as a "widespread untoward consequence of human sexuality".

Key words

Herpes Genitalis + diagnosis + drug therapy + epidemiology + etiology + therapy + prevention and control + vaccination; Signs and Symptoms; Serologic Tests; Polymerase Chain Reaction; Recurrence; Immunocompromised Host; Infant, Newborn; Pregnancy Complications; Acyclovir; Antiviral Agents

Recent data encourage the definition of genital herpes as a chronic, nearly always active herpes simplex virus (HSV) infection of sacral ganglia, that may appear bilaterally and in more ganglia than previously thought (1).

Epidemiology

Genital herpes represents one of the most prevalent sexually transmitted infection and the most frequent cause of genital ulcer disease in the general populations of developed countries (2). It is caused by HSV type-2 (HSV-2) in 60-80% of cases, with HSV-1 infection causing the remainder (3). Genital herpes caused by HSV-1 is on the rise and accounts for nearly half of new cases in developed countries, especially among young adults of white ethnicity in the UK. This may be due to a reduced exposure to HSV during childhood, and to increasing practice of oral sex (4). The increased genital

HSV-1 positivity rate of 64% in young women, aged 24 years or younger, is likely to affect the overall positivity rates among their local population (5). Since genital HSV-1 infections have higher risk for transmission from mother to infants during delivery than HSV-2, they account for 30% of all cases of neonatal herpes.

Serological studies have found prevalence of HSV-2 in the general population of developed countries to be up to 25%; a total number of 29 million cases in men, and 12.3 million cases of HSV-2 infection in women of Eastern Europe and Central Asia (WHO 2003) (6). The presence of HSV-2 antibodies almost always indicates a genital infection, while presence of HSV-1 antibodies may also indicate orolabial herpes, depending on the clinical presentation. About 1 in 5 adults in the USA have genital herpes, but only 9% of them are aware of their infection (7). Underdiagnosing is increasing, being the main obstacle for effective control of transmission. In one study, HSV-2 was isolated from genital specimens in about 72% of persons with asymptomatic genital herpes (8).

Etiology and pathophysiology

Genital herpes is caused by herpes simplex viruses (HSVs). There are two types of HVSs: type-1 (HSV-1) which has primarily and traditionally been associated with oro-facial infections, and HSV type-2 (HSV-2) with anogenital, sexually transmitted infections. However, differentiation of HSV-1 from HSV-2, based on anatomical site of infection is not absolute, since genital herpes may frequently be caused by HSV-1 as a consequence of orogenital sexual relationships. Infection occurs during a close contact with mucous membrane, abraded skin lesions or mucosal secretions of a person who has genital lesions, or is shedding HSV. Viral invasion of epithelial cells happens at the site of exposure, and then HSV ascends via sensory nerves to the sacral root ganglia and enters a lifelong latent state. Recurrent episodes are due to HSV reactivation. Viruses travel along the sensory neurons to the corresponding mucocutaneous area (3). Intermittent reactivation of virus from sacral ganglia and lytic replication in the epithelium is thought to result in viral shedding at the genital mucosa, with or without symptoms, predominantly at the site of primary acquisition (3). The anatomic patterns of genital HSV reactivation, and the resulting immune response for clearing the virus, may increase the risk of sexual HSV transmission and the acquisition of viral co-pathogens, e.g., a human immunodeficiency virus (HIV) type 1. HSV-2 has been linked to the acquisition and transmission of HIV-1. Genital ulcers from HSV may facilitate the transmission of HIV through mucosal disruptions. The infiltration of CD4+ lymphocytes in herpetic lesions creates targets for HIV attachment and entry.

It has been shown that HSV reactivates in the genital tract in more than 90% of persons, while nearly one-half of HSV shedding days are without symptoms. The most common sites of viral shedding in women are vulva, cervix and perianal region. More recent studies suggest that HSV-2 reactivates at regions overlapping genital sites from multiple ganglia. Infection of the contralateral ganglia may occur during primary or recurrent infection. Thus, HSV shedding occurs nearly continuosuly at widely spaced regions of the genital tract (9).

The clearance of virus from mucosal surfaces probably depends on a number of factors, including the local immunologic response. It has been demonstrated that HSV-specific cytotoxic $CD8^+$ T cells accumulate near sensory nerve endings in genital skin during subclinical HSV-2 reactivation. Moreover, it has recently been shown that HSV-specific $CD8^+$ T cells persist at the site of a genital ulceration for more than 6 months (10), which may explain why some episodes of HSV shedding are asymptomatically cleared within hours, while others progress to genital lesions (9).

If each episode of reactivation elicits a persistent immune response to clear the virus, the patterns of widespread reactivation may explain the role of HSV-2 in increasing the risk of HIV-1 acquisition (9).

Clinical manifestations

First infection with either herpes simplex virus type 1 (HSV-1) or type 2 (HSV-2) is termed primary infection and results in either symptomatic disease at the site of viral entry (i.e. on the face or genital area), or asymptomatic, and thus unrecognized infection. In addition, there may be systemic symptoms, similar to other acute viral illnesses (11). The primary HSV genital infection can be asymptomatic or characterized by the appearance of painful mucocutaneous vesicles on the genital area, 4 to 7 days after sexual intercourse, which evolve into erosions and crusts. Spontaneous healing occurs in 5 to 10 days (12).

The lesions and natural history of the resulting HSV-1 and HSV-2 infections are very similar. However, because HSV-2 is almost always associated with genital disease, whereas HSV-1 is associated with both oro-pharyngeal and genital disease, acquisition of HSV-1 usually results in lesions of the oro-pharynx and around the mouth and on the lips and chin, but occasionally the eyes are also affected. Sexual transmission of HSV most often causes infection of the genital mucosa, genital skin

(penile and labial) and perigenital region. Viruses from genital secretions may also infect other areas, including the eyes, oropharynx and rectal mucosa (13).

Primary herpetic infection, when a HSV sero-negative person acquires HSV-1 or HSV-2, is usually the most severe manifestation of infection. Following primary exposure to HSV-1 children may develop severe oro-pharyngitis. Such episodes resolve spontaneously, but recurrences are possible (infection persists in the cervical ganglia). Similarly, if an individual has not been exposed to HSV-1 in childhood, he or she may develop severe genital lesions following sexual exposure to HSV-2 later in life. As with HSV-1 infections, primary HSV-2 infections resolve spontaneously, but recurrences are likely to occur (the infection persists in the sacral ganglia) (13).

In cases of initial, non-primary infection, i.e. when a person with antibodies to HSV-1 subsequently acquires HSV-2, the genital infection is less severe, but it is also associated with recurrences.

In most cases of genital herpes (80–90%) the disease progresses subclinically, but may become symptomatic at any time (13).

The incubation period of both HSV-1 and HSV-2 is usually from two to 10 days (up to four weeks). Therefore, the first episode may indicate either recent or long-lasting infection. Recurrent herpetic infection is associated with reactivation of the virus. The recurrences arise per month. The localization of the primary and recurrent lesions usually coincides. Both oral and genital herpes are manifested by acute recurrences followed by varying periods of latency, when the virus remains in a non-multiplying episomal form in the nuclei of the neurons within the ganglia. Commonly, each episode or recurrence is characterized by a patch of redness at the site of the recurrence, followed by a localized papular and then a vesicular rash. The vesicles contain a clear fluid that contains many thousands of infectious viral particles. These vesicles burst, forming shallow ulcers or erosions that eventually crust and heal spontaneously without leaving scars. These episodes usually last less than 10 days, but may be prolonged as a result of secondary bacterial infection or immunosuppression (13).

The main clinical symptoms in females are: papular and/or vesicular rash on genitals or thighs; genital ulcerations; dysuria; vaginal and/or cervical discharge; dyspareunia; inguinal discomfort. The main clinical manifestations are: papular and vesicular rash on vulva, perineum, thighs; urethritis; vaginal discharge; dysuria; dyspareunia; hyperemia of the mucous membranes of vulva and vagina; cervicitis (13).

The main clinical symptoms in males are: papular and/or vesicular rash on genitals or thighs; genital ulcerations; perineal pain; dysuria; inguinal discomfort. The main clinical manifestations are: papular and vesicular rash on thighs, penis, perineum; urethral discharge; dysuria (13).

The main clinical symptoms in newborns (and/or infants) are: vesicular skin rash; keratoconjunctivitis; mild pyrexia; lethargy; convulsions. The main clinical manifestations are: vesicular skin rash; keratoconjunctivitis; mild pyrexia; irritability; convulsions (13).

The main clinical complications of genital herpes infections are: viral meningitis; radiculomyelopathy with involvement of sacral nerves; extensive vesicular skin rash; increased risk for acquiring and shedding human immunodeficiency virus (HIV). The main clinical complications of genital herpes infections in newborns (and/or infants) are: generalized skin rash; encephalitis; infant death (13).

Genital and oral herpes are life-long infections. Neonatal herpes (including neonatal encephalitis) as well as increased risk for acquiring and shedding human immunodeficiency virus (HIV) are the most serious consequences of genital herpes infection (14).

Reactivation of latent HSV leads to subclinical (asymptomatic shedding) or symptomatic genital mucocutaneous outbreaks. Symptomatic recurrent flares occur in 20 to 50% of patients with anti-HSV antibodies (12). When infection involves the genital region, subsequent recurrence frequency is greater for HSV-2 than HSV-1 infection (11). Genital HSV-1 infection leads to less frequent outbreaks (mean recurrence rate: 1.3/ year) than HSV-2 infection (15). Recurrences are milder than the primary infection, characterized by more limited and less painful unilateral (or bilateral) lesions, without systemic symptoms (11). Following a symptomatic first episode of HSV-2 genital infection, a median recurrence rate is four recurrences during the first year.

The rate of recurrence usually decreases over time, but in about one quarter of patients it increases. Immunosuppressed patients have more severe and frequent recurrences. The recurrence rate is lower in patients with recurrent genital herpes (12).

Diagnosis

Clinical diagnosis of genital herpes is non-specific and insensitive. Since the classic herpes is not a typical herpes, and that majority of patients have atypical lesions, dependence on clinical diagnosis alone should be maximally avoided (2).

Laboratory diagnosis

Laboratory confirmation should be done in all persons with suspected genital herpes. Methods used for the diagnosis could be classified into direct detection of HSV in lesions and serology testing.

HSV detection

In all patients with recurrent genital ulcers of unknown etiology and actual lesions lasting more than 4 days, diagnostic confirmation is recommended by performing assays that directly detect HSV in genital specimens. Testing swabs should be taken from the base of the lesion (ulcer or unroofed vesicle) and transported in viral medium (11). HSV detection could be done by using virus isolation in cell culture or HSV DNA detection in muco-cutaneous swabs by using nucleic acid amplification tests (NAATs) e.g., real time polymerase chain reaction (PCR) (11,13,16). Both methods allow virus typing. HSV detection using PCR has been shown to be the method of choise (11).

Nucleic acid amplification tests

HSV detection by real-time PCR is superior compared with virus culture and represents the gold standard for laboratory diagnosis of genital herpes, because it increases HSV detection rates in mucocutaneous swabs by 11-71% compared with virus culture (3). PCR increases sensitivity from average 70%, using viral culture, to almost 100% (17). Moreover, it allows less strict sample transportation conditions. When compared with traditional PCR, real-time PCR allows detection and virus typing in a single test. It also allows simplified conditions of performance and lowers the risk of cross contamination (11,13). A more recent study has shown that when compared with virus culture, HSV-1 and HSV-2-type-specific PCR conducted with real time, has significantly improved the turnaround time, with almost 70% of tests having been reported in less than 24h (16). Thus, it significantly improved the diagnosis of genital herpes without additional cost. In order to provide results at the preferred costs, real-time PCR assays must be available in those laboratories currently performing a significant number of PCR investigations for different purposes (16). The main disadvantage of real-time PCR assays is that they cannot test virus resistance using routine methodologies (11).

Viral isolation in cell culture

In the past, virus isolation in cell (e.g., human fibroblasts) culture has been the "cornerstone" of HSV diagnosis (13). The isolation rate from actual lesions (swab/scraping must be taken from active lesions during viral shedding, which, on average, lasts 4 days) ranges between 90% from vesicular or pustular lesions, 70% from ulcers to 27% at the crusting stage. Its advantages include high specificity and detection of active infection within a clinical lesion. It allows virus typing and antiviral sensitivity testing by routine methodologies (11). The characteristic cytopathic effect of HSV in tissue culture appears within 24-72 hours, but may take up to five days (13). It is not only being slow (7-10 days) and less sensitive than PCR, but rather labour intensive and expensive. Its storage and transport conditions affect the sensitivity (11).

When using cell culture, specific HSV typing can be done on the infected cell cultures by direct immunofluorescence (DIF) (using fluorescein isothiocyanate or immunoperoxidase-labeled type-specific monoclonal antiodies), or by testing supernatant by nucleic acid amplification tests (NAATs) with specific primers (13).

Alternative tests for virus detection in settings with limited laboratory facilities

Alternative assays for virus detection are not generally recommended, since they are 10-100 fold less senstive when compared with virus culture (11). They offer detection of HSV antigen in settings with limited laboratory facilities.

Antigen detection

Viral antigen detection can be performed on swabs by enzyme immunoassay (EIA) or by direct immunofluoresence (DIF) (by using fluorescein-labeled monoclonal antibodies) on smears/tissue sections.

Antigen detection enzyme immunoassay may offer a rapid diagnostic alternative in symptomatic patients with typical presentations, when sensitivity may be even higher than that of virus culture (but lower for cervical and urethral swabs). However, most commercially available EIAs do not differentiate between serotypes (11, 13).

Direct immunofluorescence can be a valuable diagnostic tool when performed in populations with high-prevalence of genital herpes. For asymptomatic patients its sensitivity may be less than 50% in comparison with cell culture (11,13).

HSV serology testing

Serologic tests detect antibodies to HSV in the blood, and indicate an ongoing latent infection. Unfortunately, serological tests (type- or non-type-specific) alone, cannot suggest the etiology of a persisting genital lesion with any degree of certainty (13).

Traditionally, serologic tests for anti-herpes simplex virus (HSV) antibodies have been of a limited value for the treatment of patients with genital herpes (18,19). Although the number of genital HSV-1 infections has been increasing, HSV-1 seropositivity is usually associated with orolabial infection. Since HSV-2 infection, limited to the oral mucosa, occurs rarely, HSV-2 seropositivity is considered synonymous for genital infection. While a positive HSV-2 serologic test result does not exclude other causes of genital eruptions, it may be useful to justify antiviral treatment in selected patients. On the other side, complete absence of seropositivity may be useful to exclude genital herpes. It has been reported that at least 12% of patients with a clinical history of genital herpes have no serologic evidence of infection (20). One study reported that serologic testing contributed to diagnosis in 79% of patients with recurrent genital eruptions of unknown etiology (21). As HSV-1 recurs less frequently than HSV-2, specific typing has not only diagnostic and therapeutic, but a prognostic utility as well. Moreover, many cases of genital herpes are transmitted by persons who are unaware of the fact that they are infected, or do not know how to recognize the symptoms. The great majority of these persons intermittently shed the virus. More than half of "asymptomatic" patients can be taught to recognize the symptoms. Thus, determination of specific serostatus allows more comprehensive counseling and better management (11,18,23).

Type-specific and non-type-specific antibodies to HSV develop during the first weeks after infections, and during this period, a "window", the test results will be negative. Although the detection of HSV-specific immunoglobulins-class M (IgM) in the absence of IgG response (type-specific IgG becomes detectable 2 weeks to 3 months after the onset of symptoms) is theoretically useful for detection of recent herpes infection (19), IgM response will also be detected in a third of patients with recurrent genital herpes caused by HSV-2. Thus, detection of IgM represents a poor indicator of recent infection (13). Moreover it has limited availability in routine diagnostic practice (11).

Traditionally, the epidemiologic gold standard has been the Western blot analysis (sensitivity > 94% and > 99%, whereas specificity > 94% and > 99% for HSV-1 and HSV-2, respectively), but being rather expensive, it is available only in a few research centers. The majority of patients who are seropositive for herpes simplex virus type 2 (HSV-2) by Western blot analysis are unaware of their symptoms (unrecognized infection) or have a subclinical infection.

Regarding serologic immunoassays for HSV antibodies that were commercially available in 1991, these tests suffered from poor sensitivity and specificity. The tests used relative reactivity against HSV-1 and HSV-2 to determine which subtype was dominant. Both types share many same antigens. The overall sensitivity and specificity was about 70%. The tests were often unable to detect antibodies to HSV-2 in patients with antibodies to both viral subtypes.

A new generation of enzyme immunoassays with a high degree of sensitivity (88% for HSV-1 and 95-98% for HSV-2) and specificity (99% for HSV-1 and 97-98% for HSV-2) have been developed and they are commercially available for nearly two decades: Gull HSV-1, HSV-2 gG IgG and Gull HSV-1, HSV-2 gG IgM type specific ELISA (Gull Laboratories' Salt Lake City, Utah, USA); POCkit™ HSV-2 (Diagnology, UK); Cobas® Core HSV-2 IgG EIA (Roche, Basel, Switzerland). The results are rapidly obtained and inexpensive. These tests are based on the antigenically unique, type-specific glycoproteins gG-2 for HSV-2 and/or gG-1 for HSV-1. The POCkit HSV-2 Rapid Test only determines HSV-2 seropositivity and provides rapid (6 minutes) results with sensitivity of 96% and specificity of 97% compared with the Western blot analysis (22).

Currently, several commercial type-specific HSV serologic tests with reported sensitivity > 95% and specificity > 97% are available, e.g.: Focus HerpeSelect ELISA and Immunoblot; Katon HSV-2 assay. Regarding rapid point-of-care tests, several tests are commercially available, e.g., Biokit HSV-2 assay, previously POCkit™ HSV-2, with sensitivity and specificity > 92% (11). Rapid, point-of-care serologic tests for sexually transmitted infections can be used outside the routine laboratory and in less sophisticated clinical settings. The first FDA-cleared HSV-2 rapid test (POCkit) for whole blood and serum was described in 1999, but in recent years, new assays with native gG-2 have been developed, such as the lateral-flow immunochromatographic assay (LFIA), which represents a rapid, sensitive and specific point-of-care device for detection of herpes simplex virus type-2-specific IgG antibodies in serum and whole blood. The sensitivity of the HSV-2 LFIA compared to that of the HerpeSelect ELISA (which uses recombinant gG-2 antigen) was 100% with specificity of 97.3% (23).

In conclusion, HSV-type-specific serological testing is a useful diagnostic tool, but it is not recommended for routine use in all asympthomatic patients. Moreover, it is valuable only if it is done

according to endorsed consensus guidelines. According to the 2010 European guidelines for the management of genital herpes (11), type-specific serologic testing is indicated in the following groups:

1. patients with history of recurrent or atypical genital disease of unknown etiology when direct virus detection methods have been negative;
2. patients with first-episode genital herpes at the onset of symptoms, where differentiation between primary and established infection indicates counseling and management (the absence of HSV IgG against the virus type recovered in the genital lesion is consistent with the primary infection);
3. sexual partners with genital herpes, where concerns are raised about transmission;
4. asymptomatic pregnant women, where there is a history of genital herpes in the partner, since clinical diagnosis of genital herpes at the time of delivery correlates relatively poorly with HSV detection from genital sites by either culture or PCR and fails to identify women with asymptomatic HSV shedding;
5. persons with high-risk sexual behaviour;

Testing of HIV-infected patients and HIV-infected pregnant women is not routinely recommended (11).

Management

First-episode genital herpes

First episodes of genital herpes are frequently associated with general and local complications. Therapy should be commenced as soon as possible and on clinical suspicion alone.

Antivirals

Currently, no therapy alters the natural course of genital herpes infection. Acyclovir, valacyclovir and famciclovir are all effective only in reducing the severity and duration of episode.

Oral antiviral drugs should be given within the first 5 days of the episode, or while new lesions are still forming. The only indication for the use of intravenous therapy is when the patient is unable to swallow or tolerate oral medications because of vomiting. Being less effective than oral agents, topical agents should not be recommended. Patients with sustained systemic symptoms, new lesion development, and complications, should continue therapy beyond five days. The recommended regimens are presented in Table 1. (11).

Supportive measures

Saline bathing and the use of topical anaesthetic agents e.g., lignocaine of gel or ointment should be recommended (11).

Counseling

When counseling patients with first episode genital herpes, the following issues should be discussed during one or two sessions: transmission risks including subclinical shedding; limited impact of condoms and antivirals; information about pregnancy is important both to men and women.

Management of complications

Hospitalization may be required for the following complications: urinary retention, meningism, superinfection of lesions (by the rule, candida occurs during the second week) (11).

Recurrent genital herpes

Strategy for managing genital herpes recurrences includes supportive therapy only, episodic antiviral treatment, and suppressive antiviral therapy. It may vary according to recurrence frequency, symptom severity, and relationship status, for most patients, being supportive only, with local saline bathing or topical petroleum gel.

Episodic antiviral treatment

Oral acyclovir, valacyclovir and famciclovir are effective at reducing the duration and severity of recurrent genital herpes. No advantages of one therapy over another, or extended 5-day treatment over ultra-short therapy were reported. The recommended regimens – all five days long – are presented in Table 1. (11).

Suppressive therapy

Suppressive therapy should be given to patients with a recurrence rate equivalent to ≥6 recurrences/year, but even patients with a lower rate of recurrence will also benefit from a reduced rate of recurrence with treatment.

Safety and resistance in patients on long-term therapy have been achieved through 18 years of continuous surveillance. Even after prolonged periods of suppression, many patients will find no significant improvement in disease frequency or severity, upon discontinuation and reassessment. The recommended regimens are presented in Table 1. (11).

The optimal total daily dose of suppressive acyclovir therapy is 800 mg, and full suppressive effect is usually only obtained five days into treatment. It is very important to mention that once-daily acyclovir does not suppress genital herpes recurrences. Therapy should be discontinued after a maximum of a year of continuous antiviral therapy to reassess recurrence frequency, providing the patient is willing to accept this course of treatment. A small number of patients will experience a reduction in recurrence frequency compared with pre-suppression symptomatic

Table 1. Antiviral therapy in the management of the immunocompetent individuals with genital herpes

Therapy	**Duration**		**Drug**		
Genital herpes	Course	Days	Acyclovir	Valacyclovir	Famcyclovir
First-episode				Daily regimen	
	5-day course	5	200 mg x 5 400 mg x 3	500mg x2	250 mg x 3
Recurrent					
	5-day course	5	200 mg x 5 400 mg x 3		
	Short course	1			1000 mg x2
		2	800 mg x 3		
		3		500 mg x 2	
	Suppression	≤ 365	200 mg x 4 400 mg x 2	250 mg x 2	
< 10 per year				500 mg x 1	250 mg x 2
> 10 per year				250 mg x 2 1000 mg x 1	

levels. The minimum period of assessment should include two recurrences. The treatment should be restarted in patients who continue to have significant symptoms (11).

To prevent clinical symptoms, short courses of suppressive therapy may be given e.g. for holidays, exams, etc.

Viral shedding and transmission during suppression therapy
Acyclovir, valacyclovir and famcyclovir all suppress symptomatic and asymptomatic viral shedding. Interestingly, partial suppression of viral shedding does not necessarily correlate with reduced transmission. However, it has been shown that suppressive therapy with valacyclovir 500 mg a day (in those with 10 or fewer recurrent episodes per year), significantly reduces transmission in serodiscordant couples (24), thus, it should be considered in addition to the use of condoms and selective sexual abstinence.

Management of HSV in immunocompromised and HIV positive patients

Management of the first episode of HSV
In patients with advanced HIV infection (not in HIV positive patients with normal CD4+ T lymphocyte counts), or in those in whom new lesions continue to form from 3 to 5 days, a higher dose should be considered. Treatment should be given for 5-10 days, or at least until all lesions have re-epithelialized which will often exceed the usual 10 day treatment that is given to HIV negative patients. If fulminant disease occurs than intravenous aciclovir should be administrated. The recommended initial doses are given in Table 2. (11).

Management of recurrent disease
Standard doses of antiviral drugs should be effective in those without evidence of immune failure. In those with advanced disease, it may be necessary to double the standard dose and to continue therapy beyond 5 days. The recommended doses are given in Table 2. (11).

Suppressive therapy
Suppressive antiviral therapy for HSV is effective and well tolerated. Standard suppressive doses of acyclovir are effective. Valacyclovir is more effective when given twice daily, compared to once daily dose (1000 mg) (25). If these agents are not successful in controlling the disease, then famciclovir 500 mg twice a day should be tried (Table 2.).

Table 2. Antiviral therapy in the management of immunocompromised and patients with advanced HIV and genital herpes

Therapy	Duration		Drug		
Genital herpes	Course	Days	Acyclovir	Valacyclovir	Famcyclovir
First-episode				Daily regimen	
	10-day course	5 - 10	200-400 mg x 5 400-800 mg x 3	500-1000 mg x 2	250-500 mg x 3
Recurrent					
	10-day course	5 - 10	400 mg x 5 800 mg x 3		
	Suppression	≤ 365	400 mg x 2	500 mg x 2	500 mg x 2

Management of recalcitrant herpes in immunocompromised individuals

Being rare in immunocompetent individuals, clinically refractory lesions of genital HSV represent a major problem in patients with severe immunodeficiency. Algorithms for treatment in such situations include the following: confirmation of genital herpes by PCR or culture; increased dose of acyclovir to 800 mg 5x daily, or orally taken valacyclovir of 1000 mg twice daily, or famciclovir of 750 mg twice daily; isolation of virus by culture and sensitivity testing.

In patients with drug resistant genital herpes and accessible lesions, topical trifluridine or topical cidofovir gel should be given 3 times daily until complete healing. Alternatively, imiquimod cream three times weekly or topical foscarnet (2.4%) during 20 minutes twice daily should be advised. In patients with drug resistant genital herpes and non-accessible lesions, intravenous foscarnet 40 mg/kg/BW every eight hours during 2-3 weeks or until lesions heal, should be commenced (11).

HSV suppression to limit HIV progression

According to a recent randomized placebo-controlled trial in individuals with early HIV (those individuals not on HAART and with CD4+ T lymphocyte counts above 350), dually infected with HIV-1 and herpes simplex virus type-2, the standard doses of suppressive antiviral therapy (acyclovir 400 mg bid), sustained CD4+ T lymphocyte counts above accepted treatment levels, reduced the need for HAART for 2 years by 16% in the treatment group (26).

Partner management

When partner counseling, it is worth to follow the further topics: role of asymptomatic shedding in transmission of genital herpes; partner notification after type-specific antibody testing; recognition of genital herpes recurrences after counseling, which can substantially reduce HSV transmission; reduction of transmission by using condoms in association with suppressive antiviral treatment (11).

Management of pregnant women with first episode of genital herpes

Though acyclovir administration during pregnancy has not been associated with any consistent fetal/neonatal adverse effects other than transient neutropenia, the use of acyclovir or any other antiviral drug, has not been licensed during pregnancy. Since valacyclovir is the l-valine ester, safety data for acyclovir may be transferred in late pregnancy to valacyclovir (27). Famciclovir should currently be avoided (11).

First and second trimester acquisition

Management of pregnant women with first episode of genital herpes in the first or second trimester includes oral or intravenous acyclovir therapy in standard doses. Daily supressive therapy with acyclovir will provide anticipation of vaginal delivery and prevent the need for delivery by Caesarean section if starts from 36 weeks gestation (Table 3) (11).

Third trimester acquisition (IV, C)

Management of pregnant women with first episode of genital herpes during the third trimester includes Cesarean section that should be considered in all women taking oral or intravenous acyclovir suppressive therapy that should start at 36 weeks gestation (Table

Table 3. Antiviral therapy in the management of pregnant women with first episode genital herpes

Therapy	Strategy	Duration	Drug	Delivery
Genital herpes I episode	Course	Days	Acyclovir	
			Daily regimen	
I or II trimester	5-day course	5	200 mg x 5 400 mg x 3	
	Suppression	Start at 36 weeks gestation	400 mg x 3	Vaginal
III trimester	5-day course	5	400 mg x 3	
	Suppression	Start at 36 weeks gestation	400 mg x 3	Cesarean section

3.). This may prevent HSV lesions at term. The risk of viral shedding during delivery is very high, especially in pregnant women developing symptoms within 6 weeks prior to delivery. If vaginal delivery cannot be avoided, then acyclovir given during delivery intravenously to the mother and subsequently to the baby, may be considered and the pediatrician should be informed (11).

Management of pregnant women with recurrent genital herpes

The risk of neonatal herpes is low in women with recurrent genital herpes and they should be informed about it.

If there are no genital lesions at delivery, there are no indications for Cesarean section (to prevent neonatal herpes), and vaginal delivery is indicated. If there are genital lesions at delivery, there are also no indications for Caesarean section (to prevent neonatal herpes), and vaginal delivery is indicated. However, this can only be approved if fully agreed by obstetricians, neonatologists, and local medico-legal advice.

If there is a history of HSV lesions at the onset of delivery, daily suppressive acyclovir in standard doses, from 36 weeks gestation may prevent HSV lesions at term, as well as the need for delivery by Cesarean section (Table 4.) (11).

Management of recurrent HSV in early pregnancy

Administration of acyclovir for suspected acquisition of genital herpes in early pregnancy is widely advocated, despite the fact that the safety of acyclovir has not fully been established. Contrary to this, in recurrent genital herpes continuous or episodic therapy is not recommended in early pregnancy and should be avoided. Newer antivirals should also be avoided. Rarely, in severe and complicated cases, administration of acyclovir cannot be avoided, and an individual assessment should be made.

Management of HIV positive women with recurrent HSV infection

There is some evidence that HIV antibody positive women with genital HSV ulcerations may be more likely to transmit HIV infection during pregnancy than others (28). These women should be advised to take daily suppressive acyclovir from 32 weeks gestation that would reduce the risk of transmission of HIV-1 infection and increased possibility of preterm labour (Table 5.) (11).

Preventing acquisition of infection

Any strategy for prevention of neonatal herpes must involve both parents and include the following issues:

- at the first antenatal visit, all women should be asked if they, or their partner, have had genital herpes;
- female partners of men with genital herpes, but with no personal history of genital herpes, should be advised about using condoms during pregnancy especially in the last trimester of pregnancy, including abstinence from sex at the time of lesional recurrences and in the last six weeks of pregnancy;
- the effectiveness of suppressive treatment of the male partner has not been evaluated so far, thus currently it can only be recommended;
- all pregnant women should be advised to avoid orogenital contact, especially in the last trimester of

Table 4. Antiviral therapy in the management of pregnant women with recurrent genital herpes

Therapy	Strategy	Duration	Drug	Delivery
Recurrent genital herpes	Course	Days	Acyclovir	
			Daily regimen	
Early pregnancy				
III trimester	5-day course	5	400 mg x 3	Vaginal
History of lesions on delivery	Suppression	Start at 36 weeks gestation	400 mg x 3	Vaginal
Lesions on delivery				Cesarean section
No lesions on delivery				Vaginal

pregnancy;
- all women should undergo careful vulva inspection at the onset of delivery ;
- all persons, including mothers, with active oral HSV lesions or herpetic whitlow should avoid direct contact between lesions and the neonate.

Management of the neonate

If the baby was born to mother with first-episode genital herpes at the onset of labour, the following instructions should be followed after delivery:
- HSV culture of urine and stool, from the babies oropharynx, eyes and surface sites, should be taken;
- the potential benefits and risks of starting intravenous acyclovir without waiting for the results of these cultures should be discussed;
- if acyclovir is not started immediately, the neonate should be closely monitored for signs of lethargy, fever, poor feeding or lesions.

If the baby was born to mother with recurrent genital herpes at the onset of labour, the parents and health care workers should be advised to consider HSV in differential diagnosis by searching for signs of infection on the skin, eyes or mucous membranes, especially during the first two weeks of life (11).

Prevention

Biomedical strategies for the control of genital herpes such as therapeutic approaches, abstinence, monogamy, the use of condoms, or vaccination have not given satisfactory results so far, and they are in different phases of development. The greatest expectancy is developing of efficient vaccines (29).

Immunoprophylactic HSV-2 vaccines

Production of vaccines against HSV infection has been slowed down because of their ineffectiveness in men and in HSV-1 (+) women (30). Investigations conducted so far have resulted in mass vaccination among women with HSV-1,-2 (31).

Antigens for prophylactic vaccines are viral membrane glycoproteins HSV-1 gB8 and HSV-2 gD. The produced antibodies are neutralizing and protective (31).

Prophylactic HSV-2 gD2-alum-MPL vaccine consists of HSV-2 gD, alum, and MPL adjuvant (3-de-0-acyl monophosphoryl lipid A). In phase I/II, and phase III of clinical trials the vaccine has been administered intramuscularly according to -0, -1, and -6 months schedule. High safety level and high tolerance of the vaccine have been reported. Prevention of genital HSV-2 symptoms has been achieved in 73% to 74% of HSV (-) women and prevention of HSV-2 infection in 39% to 46% of HSV (-) women. Further investigations are needed to explain the role of adjuvant and sex in vaccine efficacy (31, 32).

Because the average efficacy of the vaccine in the prevention of HSV-2 infection is only 42%, it raises the question of whether partial efficacy can be beneficial. In mathematical model considering the natural course and dynamics of HSV-2 transmission, the fulfillment of two conditions is necessary to answer the questions: 1. if vaccination reduces disease transmission through

Table 5. Antiviral therapy in the management of HIV positive pregnant women with recurrent genital herpes

Therapy	Strategy	Duration	Drug	Delivery
HIV-positive and HSV-1 and/or HSV-2 positive	Course	Days	Acyclovir	
No history of genital herpes				Vaginal
History of genital herpes	Suppression	Start at 32 weeks gestation	400 mg x 3	Vaginal
Lesions on delivery				Cesarean section
No lesions on delivery				Vaginal

reducing the number of carriers, then it may have the main role in the control of HSV-2 infection; 2. universal vaccination of the female population aged 10 to 12 years, would reduce HSV-2 among general population, including men (30, 33, 34).
The perspective of prophylactic HSV-2 vaccines lies in successful termination of phase III clinical trials and their approval.
The vaccine is expected to fulfill the above-mentioned conditions having in mind that HSV-2 infection has a small probability of transmission along with a long-term infectivity (33).

Immunotherapeutic HSV-2 vaccines
The recombinant gD2-alum vaccine demonstrated fewer recurrences in a double-blind, placebo-controlled clinical trial, fewer viral culture-proven genital HSV recurrences per month, and a lower average number of recurrences during the year of the study in the vaccinated group (35).
In a double-blind, placebo-controlled clinical trial, the ICP10DPK vaccine completely prevented HSV-2 recurrences in 37.5% of patients in the vaccinated group, while 100% of patients in the placebo group had at least one recurrence 6 months after vaccination (36).

Experimental HSV-2 vaccines
Recombinant adenovirus vaccine rAdgB8 is in experimental phase of investigation on laboratory animals. The vaccine is administered intranasally and it induces good mucous immunity (37).
Vaccines HSV-2 dl5-29 and HSV-2 dl5-29-41L are also in experimental phase of investigation on laboratory animals (38).
Intranasal immunization with a proteoliposome-derived cochleate containing recombinant gD protein (AFCo1gD) conferred protective immunity against genital herpes in mice. These data may be useful in the development of a mucosal vaccine against genital herpes (39).

Final observations

Thirty years ago, in the absence of reliable serological tests and highly effective medications for diagnosis and treatment of genital herpes, herpes was defined as **"**Today's Scarlet Letter**"**. In 2000, apart from virus isolation in cell culture, that has long been regarded as the diagnostic gold standard (70% sensitivity), type-specific serologic tests and higly effective antiviral agents have been developed. However, the following questions were imputted: should we routinely recommend serologic testing in asymptomatic patients; does antiviral therapy reduce asymptomatic shedding of the virus; is sexual transmission of infection reduced by antivirus therapy; does antiviral therapy reduce the acquisitation of viral copathogens? Ten years later, we now know the answers. Type specific HSV DNA detection by real-time PCR assays (100% sensitivity) is the diagnostic test of choice for every person with recurrent genital ulcers of unknown etiology that last more than 4 days, and must be available in those laboratories currently performing a significant number of PCR investigations for different purposes. Type specific gG serology testing is indicated in all asymptomatic persons who are at increased risk for HSV infection. For those sexually active patients experiencing ≥ 6 recurrences per year, daily supressive dose of acyclovir, valacyclovir or famciclovir should be discontinued after a maximum of a year of continuous

antiviral therapy to reassess recurrence frequency. If necessary, the therapy should be restarted after at least two recurrences. In order to prevent transmission and the aquisition of viral copathogens, therapy must suppress simultaneous HSV reactivations from bilateral sacral ganglia. With such a variety of testing modalities and more aggressive therapy, we can now define genital herpes not as a **"**Scarlet Letter**",** but as the **"**Widespread Untoward Consequence of Human Sexuality**"** (1).

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Genitalni herpes

Sažetak

Definicija: Danas se genitalni herpes definiše kao unilateralna ili bilateralna hronična, uglavnom kontinuirano aktivna infekcija (jednog ili više) senzornih gangliona sakralnog pleksusa (S2,S3,S4), izazvana herpes simpleks virusom (HSV).

Epidemiologija: Genitalni herpes predstavlja jednu od najučestalijih seksualno prenosivih infekcija i najčešći uzrok anogenitalnih ulceracija u opštoj populaciji razvijenih zemalja. U 60-80% slučajeva izazivač je HSV tip-2 (HSV-2), a njime je inficirano 15-25% odraslih osoba u SAD, preko 29 miliona muškaraca i 12,3 miliona žena u zemljama Istočne Evope i Azije. U Velikoj Britaniji u 50% slučajeva izazivač je HSV tip-1 (HSV-1), a isti tip je odgovoran za razvoj 30% svih slučajeva neonatalnog herpesa. Dok se prisustvo anti HSV-2 antitela u serumu značajno (ali ne i isključivo) povezuje sa postojanjem genitalne infekcije, anti HSV-1 antitela mogu biti prisutna i kod orolabijalnog herpesa.

Etiopatogeneza: U 60-80% slučajeva izazivač genitalnog herpesa je HSV tip-2 (HSV-2). Kod 72% osoba bez simptoma, HSV-2 je izolovan iz genitalne regije. Primarna infekcija se najčešće odvija u koži i sluznicama. Iako apsolutna podela ne postoji, primarna infekcija izazvana virusom tip 1 se najčešće manifestuje orofacijalno, gingivostomatitisom, keratokonjunktivitisom, znatno ređe encefalitisom, a infekcija virusom tip 2 genitalnim ulceracijama. Do infekcije dolazi nakon bliskog kontakta sa sluznicama, lediranom kožom i mukoznim sekretima osobe koja ima genitalne lezije ili rasipa HSV asimptomatski. Na mestu kontakta virus ulazi u epitelne ćelije, da bi potom ascedento putem senzorniih nervnih završetaka dostigao do senzornih gangliona. Virus zatim ostaje nereaktivan u ćelijama gangliona, tip 1 najčešće trigeminalnog, a tip 2 sakralnog. Do reaktivacije virusa dolazi kod oko 90% inficiranih osoba. Tokom reaktivacije HSV-2 koja se simultano ili sukcesivno dešava u jednom ili više uni/bilateralnih sakralnih gangliona, virus putuje descedentno duž senzornog neurona ka odgovarajućoj mukokutanoj regiji. Nakon tzv. litičke replikacije virusa u epitelnim/epidermalnim ćelijama, započinje rasipanje virusa sa velike površine genitalne/analne regije, koje je u skoro 50% trajanja asimptomatsko, i može se okarakterisati kao pretežno kontinuirano. Najčešće se rasipanje virusa odvija sa vulve, cerviksa i perianalne regije kod žena. Rezultati novijih istraživanja pokazuju da se reaktivacija HSV-2 odvija sukcesivno ili istovremeno unutar većeg broja gangliona uni/bilateralno. Do infekcije kontralateralnog gangliona može doći za vreme primarne ali i rekurentne epizode genitallnog herpesa.

Tokom reaktivacije, lokalni imunološki odgovor (koji za cilj ima odstranjenje HSV), na mestu reaktivacije (genitoanalna regija) pospešuje prenošenje infekcije HSV i virusom humane imunodeficijencije tip-1 (HIV-1). Metu za privlačenje i prodor HIV predstavlja infiltracija CD4+ limfocita u herpetične lezije. U uslovima supkliničkog rasipanja u toku HSV-2 reaktivacije, utvrđena je akumulacija za HSV specifičnih citotoksičnih CD8+ limfocita oko završetaka senzornih nervnih vlakana u mukokutanim genitalnim regijama. Štaviše, specifični citotoksični CD8+ limfociti mogu perzistirati u blizini genitalnih ulceracija tokom vremenskog perioda dužeg od šest meseci čime se može objasniti zašto pojedine epizode rasipanja HSV protiču asimptomatski i traju samo nekoliko časova, dok u drugim lezije progrediraju do ulceracija.

Kliničke manifestacije: Primarna HSV genitalna infekcija nastaje u slučaju da prethodno HSV seronegativna osoba postane inficirana HSV-1 ili HSV-2, i u najvećem broju slučajeva predstavlja i najtežu manifestaciju infekcije. Primarnu HSV genitalnu infekciju odlikuje pojava mukokutanih vezkula lokalizovanih u genitalnoj regiji, do kojih dolazi 4 do 7 dana posle seksualnog kontakta. Vezikule potom prelaze u erozije i kraste, a spontana sanacija nastaje nakon 5-10 dana. Primarna HSV genitalna infekcija može proticati i asimptomatski. Nakon primarne infekcije HSV-1, deca mogu razviti težak oblik orofaringitisa. Ova epizoda zaceljuje spontano, ali se mogu javiti recidivi (infekcija perzistira u cervikalnom ganglionu). Analogno ovome, ukoliko odrasla osoba nije bila u detinjstvu inficirana HSV-1 ona može razviti teške genitalne lezije ukoliko do infekcije HV2 dođe u kasnijem životu. Primarna infekcija HSV-2 takođe zaceljuje spontano, ali se mogu javiti recidivi (infekcija perzistira u sakralnim ganglionima).

U slučaju početne, ali ne i primarne infekcije, koja nastaje u slučaju da prethodno HSV-1 seropozitivna osoba postane inficirana HSV-2, genitalna infekcija je po pravilu blaža ali se takođe mogu razviti recidivi.

Inkubacioni period u HSV-1 i HSV-2 infekciji obično traje od 10 dana do 4 nedelje. U najvećem broju slučajeva (80-90%), bolest progredira supklinički, ali može postati simptomatska u bilo kom vremenskom trenutku. Stoga, prva epizoda može označiti novonastalu ali i već dugo prisutnu infekciju.

Glavni klinički simptomi i znaci kod osoba ženskog pola su dizurija, disparenurija, pojačan vaginalni i cervikalni sekret, osećaj težine u ingvinumu, papulo-vezikulozni osip u predelu vulve, perineuma, nadkolenica, uretritis, hiperemija vaginalne sluznice, cervicitis.

Glavni klinički simptomi i znaci kod osoba muškog pola su disurija, bol u predelu perineuma, ureteralni iscedak, papulo-vezikulozni osip na butinama, penisu, perineumu, i pojava genitalnih ulceracija.

Glavni klinički simptomi i znaci kod novorođenčadi/male dece su blaga pireksija, letargija, vezikulozna ospa, keratokonjunktivitis i konvulzije.

Glavne kliničke komplikacije koje se mogu javiti kod obolelog od genitalnog herpesa su virusni meningitis, radikulomijelopatija sa zahvatanjem sakralnih nerava, ekstenzivni vezikulozni osip po kože i povećani rizik od nastanka HIV infekcije. Kod novorođenčadi, glavne kliničke komplikacije su generalizovana vezikulozna ospa po koži, encefalitis i smrt. Najteže komplikacije koje se mogu javiti u toku genitalnog herpesa su neonatalni herpes sa razvojem neonatalnog encefalitisa, kao i nastanak HIV infekcije sa posledičnim rasipanjem HIV.

Recidivi: Recidivantne epizode su posledica reaktivacije virusa i u početku one se javljaju mesečno. Lokalizacija lezija najčešće se podudara sa lokalizacijom promena u primarnoj epizodi. I oralni i genitalni herpes prolaze kod različit broj reciva do kojih dolazi nakon reaktivacije virusa koji ostaje prisutan u tzv. epizodalnoj formi (bez replikacija) u jedrima neurona koja se nalaze unutar gangliona. U klasičnim slučajevima, svaku epizodu recidiva karakteriše pojava lokalizovanog pločastog crvenila sa sledsetvenim razvojem papula. Vezikule su ispunjenje bistrim sadržajem i u njima se nalaze hiljade infektivnih partikula virusa. Nakon prskanja vezikula, za njima ostaju erozije, ulceracije, a potom kraste i spontano isceljivanje bez ožiljavanja. Dužina trajanja epizode recidiva je oko 10 dana, ali ona može biti znatno veća ukoliko se radi o imunokompromitovanoj osobi ili o nastaloj sekundarnoj bakterijskoj infekciji. U 20-50% svih slučajeva, recidivi protiču simptomatski. Ukoliko se radi o genitalnoj regiji, broj recidiva je veći kod HSV-2 nego kod HSV-1 infekcije. U slučaju genitalnog herpesa izazvanog HSV-1, prosečan broj recidiva iznosi 1,3 godišnje, dok je kod HSV-2 infekcije prosečan broj recidiva oko 4 u toku prve godine posle infekcije. Po pravilu recidivi protiču sa blažom kliničkom slikom u odnosu na primarnu epizodu, bez sistemskih znakova infekcije, a karakteriše ih pojava ograničenog broja manje bolnih, uni/bilateralnih lezija. Vremenom godišnja stopa recidiva opada, ali kod 30% može rasti. Imunosuprimirane osobe imaju klinički teže epizode i višu stopu recidiva u odnosu na imunokompetentne.

Dijagnoza: Nedijagnostikovani genitalni herpes se širi epidemijski. Samo 9% HSV-2 seropozitivnih osoba zna da je inficirano. Značaj postavljanja tipski specifične dijagnoze ima veliki edukativni značaj, s obzirom da 60% osoba bez simptoma nauči da prepozna i prijavi recidiv. Značaj specifične tipizacije ima veliki prognostički značaj, s obzirom da do reaktivacije HSV-2 u genitalnom traktu dolazi kod 90% svih inficiranih a da je broj recidiva genitalnog herpesa u prvoj godini posle primarne infekcije 5x veći u odnosu na HSV-1. Pre trideset godina, u odsustvu relevantnih seroloških testova i efikasne terapije, o problemu genitalnog herpesa pisano je kao o gorućem problemu, crvenim slovima (eng. *Scarlet Letter*). Kultivacija HSV (70% senzitivnost), tipski specifične serološke reakcije i antivirusna terapija označili su početak novog milenijuma ali i nametnuli sledeća pitanja: da li treba uvesti rutinsko testiranje; da li supresivna terapija prevenira transmisiju; da li supresivna terapija smanjuje rizik od HIV infekcije? Deset godina kasnije, mi imamo odgovor na ova pitanja. Zlatni dijagnostički standard za svaku osobu sa rekurentnim genitalnim ulceracijama nepoznate etiologije koje traju više od 4 dana, jeste tipski specifičan PCR u realnom vremenu (100% senzitivnost), koji mora da obezbedi svaki centar koji raspolaže ovom tehnikom. Svaku osobu za koju se

danas smatra da poseduju povišen rizik za dobijanje HSV infekcije a koja ne daje anamnezne podatke o genitalnom herpesu treba serološki testirati tipski specifičnim, tzv. gG testovima. Trenutno, nekoliko testova (senzitivnost > 95%) je komercijalno dostupno: *Focus HerpeSelect ELISA* i *Immunoblot*; *Katon* HSV-2 test. Brzi tipski specifični testovi kao što je to *Biokit HSV-2 assay*, ranije dostupan kao *POCkit™ HSV-2*, (senzitivnost i specifičnost > 92%, rezultat dostupan posle nekoliko minuta), danas imaju prednost s obzirom da se mogu izvoditi izvan laboratorija. Prvi brzi test koji je 1999. godine bio odobren od strane FDA (eng. *Food and Drug Administration*) agencije je *POCkit™ HSV*-2. Nova generacija brzih tipski specifičnih gG testova zasniva se na upotrebi nativnog gG-2 antigena, npr. LFIA test (eng. *lateral-flow immunochromatographic assay*), koji predstavlja brz, pouzdan, visoko senzitivan i specifičan metod za dokazivanje HSV-2 specifičnih IgG antitela u serumu I u punoj krvi. Senzitivnost *HSV-2 LFIA* u odnosu na *HerpeSelect ELISA* (koji koristi rekombinantni gG-2 antigen) je u jednoj studiji iznosila 100% a specifičnost 97,3%. Iako serološko testiranje predstavlja koristan dijagnostički metod, ono nije rutinski indikovano kod svakog pacijenta koji nema simptome infekcije. Prema evropskom vodiču iz 2010. godine, testiranju podležu sledeće osobe:

1. pacijenti koji daju anamnestičke podatke o rekurentnim ili atipičnim ulceracijama nepoznate etiologije, kada se metodama direktnog dokazivanja nije utvrdilo prisustvo virusa u leziji;
2. pacijenti u prvoj epizodi genitalnog herpesa u tenutku pojave prvih simptoma, kada je potrebno razlikovati primarnu od ustaljene infekcije, što ima veliki terapijski značaj (odsustvo HSV IgG protiv tipa virusa koji je izolovan iz genitalne lezije, potvrđuje primarnu infekciju);
3. seksualni partneri osoba koje imaju genitalni herpes, ukoliko postoji povećan rizik za transmisiju;
4. asimptomatske trudnice čiji partneri daju anamnestičke podatke za genitalni herpes, s obzirom da u vreme porođaja klinički postavljena dijagnoza genitalnog herpesa ne pokazuje značajnu korelaciju sa direktnom detekcijom (kako putem PCR tako i kultivacijom), virusa u genitalnoj regiji, što u tom trenutku otežava tj. onemogućuje identifikaciju žene koja asimptomatski rasejava virus;
5. osobe sa visoko rizičnim seksualnim ponašanjem;

Rutinski testirati sve HIV-om inficirane osobe i HIV-om inficirane trudnice nije opravdano.

Lečenje u prvoj epizodi genitalnog herpesa: Često dolazi do pojave opštih i lokalnih komplikacija, iz tog razloga lečenje treba započeti odmah i kod postojanja isključivo klinički postavljene sumnje na genitalni herpes. Primenom antivirusnih lekova aciklovira, valaciklovira ili famciklovira može se isključivo smanjiti težina i/ili broj recidiva. Njih treba početi uzimati oralnim putem odmah, unutar prvih 5 dana prve epizode ili sve dok se stvaraju nove promene. Intravenski se antivirusni lekovi daju samo ukoliko pacijent otežano guta ili povraća, lokalno ne treba primenjivati antivirusnu terapiju. U slučaju održavanja sistemskih simptoma i znakova, pojave novih lezija ili komplikacija, lečenje treba nastaviti i posle petog dana lečenja, a preporučeni terapijski protokoli su izneti u Tabeli 1.

Lečenje recidiva: Lečenje može biti isključivo zasnovano na lokalnoj nezi (kupke u slanim rastvorima; aplikacija petrolej želea) ili se može uključiti i antivirusna terapija, kratkotrajna epizodna ili dugotrajna supresivna, koja se pokazala bezbednom i nakon 18 godina kontinuirane primene. Supresivna terapija se daje najčešće osobama sa ≥6 recidiva godišnje. Nakon najdužeg perioda od godinu dana kontinuirane terapije, treba je prekinuti a ukoliko se proceni racionalnim, ponoviti je tek pošto uslede najmanje dva nova recidiva. Supresivni efekat se može postići tek nakon petog dana lečenja. Optimalna ukupna dnevna doza aciklovira koja ima supresivni efekat iznosi 800 mg, ali se pri tome supresivni efekat ne može postići jednokratnim već dvokratnim ili višekratnim davanjem aciklovira (Tabela 1).

Lečenje imunosuprimiranih i HIV pozitivnih osoba: Kod osoba sa težim stepenom imunosupresije lečenje treba da traje duže od 5 dana a standardne doze za lečenje primarne epizode i standardne doze za lečenje recidiva treba povećati pa i udvostručiti (Tabela 2). Supresivna terapija je efikasna u standardnim dozama, s tim što je valaciklovir efikasniji kod dvokratnog davanja a ukoliko terapija ne dâ zadovoljavajući efekat, može se dati famciklovir (Tabela 2).

Terapijska tvrdokornost: U slučaju da se sumnja na postojanje genitalnog herpesa rezistentnog na primenjenu terapiju, treba potvrditi postojanje infekcije metodom PCR ili kulturom, povisiti dozu aciklovira na 800 mg 5x dnevno i, nakon izolacije virusa, izvesti testiranje osetljivosti. Ukoliko se potvrdi rezistencija, tada se na promene ukoliko su dostupne aplikuje trifluridin ili cidofovir gel 3x dnevno do kompletnog isceljenja. Alternativno se može dati imikviimod krem 3x nedeljno ili minutna lokalna primena foscarneta 2,4% u trajanju od po 20 minuta 2x dnevno. Ukoliko promene nisu dostupne, foscarnet se daje intravenski u dozi od 40 mg/kg/TT svakih 8 časova tokom 2-3 nedelje sve do potpunog izlečenja.

Lečenje prve epizode genitalnog herpesa kod trudnica: Iako nije zvanično odobrena primena nijednog antivirusnog leka u trudnoći, aciklovir se koristi za lečenje prve epizode genitalnog herpesa za vreme čitave trudnoće, valaciklovir u kasnoj trudnoći, dok primena famciklovira u trudnoći valja izbegavati. Ukoliko do infekcije dođe u prvom ili drugom trimestru trudnoće, lečenje se zasniva na davanju aciklovira

u standardnim dozama. Supresivna dnevna terapija aciklovirom, ukoliko započne od 36. gestacijske nedelje, može da prevenira pojavu genitalnih lezija u vreme porođaja i tako omogući vaginalni porođaj (Tabela 3). Ukoliko do infekcije dođe u trećem trimestru, opasnost od rasipanja virusa za vreme porođaja je velika i u svim slučajevima bi porođaj trebalo obaviti carskim rezom. Supresivna dnevna terapija aciklovirom, ukoliko započne od 36. gestacijske nedelje, može da prevenira pojavu genitalnih lezija u vreme porođaja (Tabela 3). Ukoliko se trudnica ipak porodi vaginalnim putem, lečenje se zasniva na davanju u toku porođaja aciklovira intravenski i majci i novorenčetu.

Lečenje recidiva genitalnog herpesa kod trudnica: Trudnici sa recidivantnim genitalnim herpesom na prvom mestu treba predočiti da je rizik od razvoja neonatalnog herpesa mali i da se porođaj može obaviti vaginalnim putem. U slučaju da je trudnica u prethodnim trudnoćama u vreme porođaja imala promene nalik na genitalni herpes, supresivna dnevna terapija aciklovirom, ukoliko započne od 36. gestacijske nedelje, može prevenirati promene za vreme porođaja i potrebu za carskim rezom (Tabela 4).

Lečenje recidiva genitalnog herpesa aciklovirom u ranoj trudnoći nije poželjno i treba ga izbeći, a to se odnosi i na ostale antirusne lekove.

HIV-pozitivnoj trudnici sa recidivantnim genitalnim herpesom supresivna dnevna terapija aciklovirom ukoliko započne od 32 gestacijske nedelje može prevenirati prevremeni porođaj i smanjiti rizik od prenošenja HIV infekcije (Tabela 5).

Prevencija neonatalnog herpesa: Algoritam za prevenciju perinatalne infekcije moraju biti uključena oba partnera i on podrazumeva sledeće:

- U toku prve prenatalne kontrole, svaku trudnicu treba pitati za ličnu i partnerovu anamnezu o postojanju genitalnog herpesa;
- Trudnicama koje nemaju ličnu anamnezu o genitalnom herpesu, ali čiji partneri imaju genitalni herpes, treba predočiti potrebu za upotrebom kondoma za vreme trudnoće, naročito tokom poslednjeg trimestra, i apstinencije od seksa za vreme recidiva herpetičnih promena i tokom poslednjih šest nedelja trudnoće;
- Sve trudnice treba da izbegavaju orogenitalne kontakte naročito tokom poslednjeg trimestra;
- Ukoliko je trudnica HSV seronegativna, u nedostatku opsežnijih ispitivanja terapijske efikasnosti, supresivna antivirusna terpija ostaje samo preporuka muškom partneru koji ima genitalni herpes;
- Svakoj trudnici treba obaviti detaljnu inspekciju vulvarne regije u vreme porođaja;
- Sve osobe, uključujući i porodilju, koje imaju aktivne oralne herpetične lezije ili herpetične promene lokalizovane na drugim delovima tela uključujući i prste, treba instruisati da izbegavaju direktan kontakt između lezija i novorođenčeta.

Ukoliko je trudnica u fazi prve epizode genitalnog herpesa porođena vaginalnim putem, predloženi algoritam podrazumeva sledeće:

- Dokazivanje HSV u urinokulturi, koprokulturi i kulturama briseva uzetih iz orofaringsa, konjuktiva i kože novorođenčeta;
- Procenu koristi i rizika od započinjanja intravenskog davanja aciklovira novorođenčetu pre dobijanja rezultata traženih kultura;
- Intervenciju u slučaju postojanja letargije, groznice, odbijanja hrane ili lezija suspektnih na genitalni herpes kod novorođenčeta, ukoliko davanje aciklovira nije odmah započeto.

Ukoliko je trudnica u fazi rekurentne epizode genitalnog herpesa porođena vaginalnim putem, potrebno je uputiti roditelje i nadležne zdravstvene radnike da kod novorođenčeta, naročito tokom prve dve nedelje života, obrate posebnu pažnju na svaki eventualno prisutni znak koji bi ukazivao na infekciju kože, očiju ili vidljivih sluznica, te da isključe HSV infekciju.

Prevencija: Matematički model predviđa da će HSV univerzalna vakcinacija svih devojčica uzrasta od 10 do 12 godina redukovati prevalenciju genitalnog i neonatalnog herpesa u opštoj populaciji.

Zaključak: Sa ovom doktrinom koja prvenstveno podrazumeva dijagnostički imperativ i agresivnije lečenje, mi danas ne govorimo o genitalnom herpesu kao „goruće problemu", nego kao „masovnoj posledici ljudske seksualnosti".

Ključne reči

Genitalni herpes + dijagnoza + medikamentna terapija + epidemiologija + etiologija + terapija + prevencija i kontrola + vakcinacija; Znaci i simptomi; Serološki testovi; Lančana reakcija polimeraze; Novorođenče; Komplikacije u trudnoći; Aciklovir; Antivirusni lekovi