

Optimal management of genital herpes: current perspectives

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Abstract: As one of the most common sexually transmitted diseases, genital herpes is a global medical problem with significant physical and psychological morbidity. Genital herpes is caused by herpes simplex virus type 1 or type 2 and can manifest as primary and/or recurrent infection. This manuscript provides an overview about the fundamental knowledge on the virus, its epidemiology, and infection. Furthermore, the current possibilities of antiviral therapeutic interventions and laboratory diagnosis of genital herpes as well as the present situation and perspectives for the treatment by novel antivirals and prevention of disease by vaccination are presented. Since the medical management of patients with genital herpes simplex virus infection is often unsatisfactory, this review aims at all physicians and health professionals who are involved in the care of patients with genital herpes. The information provided would help to improve the counseling of affected patients and to optimize the diagnosis, treatment, and prevention of this particular disease.

Keywords: herpes simplex virus, epidemiology, infection, antiviral therapy, laboratory diagnosis, prevention

Herpes simplex virus

Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are classified within the genus Simplexvirus that belongs to the subfamily Alphaherpesvirinae within the family Herpesviridae. Both are neurotropic DNA viruses with an envelope, have a size of 150–200 nm, and are characterized by low environmental resistance.¹ An electron micrograph in Figure 1 shows the composition of herpes simplex virus (HSV) which is comparable for both types. The viral double-stranded DNA genome with a length of 152 kb encodes at least 84 different structural and nonstructural proteins.² The viral protein capsid comprises 162 capsomers and has an icosahedral structure. Viral genome and capsid are summarized under the term nucleocapsid. The surrounding lipid envelope consists of host cell components and virus-encoded glycoproteins. Between nucleocapsid and outer envelope, a protein layer referred to as tegument is situated. The replication of herpesviruses is a complex process characterized by the cascade-like sequential expression of α , β , and γ genes.³ This process mainly takes place within the nucleus of the infected host cells. The sequence homology between the genome of HSV-1 and HSV-2 is ~40%, leading to nearly 85% homology of gene regions encoding virus-specific proteins. Thus, both viruses are biologically similar, and their antigens show high cross-reactivity. Type-specific epitopes are present on the surface glycoproteins gG (HSV-1 and HSV-2)⁴ and gC (HSV-1).⁵

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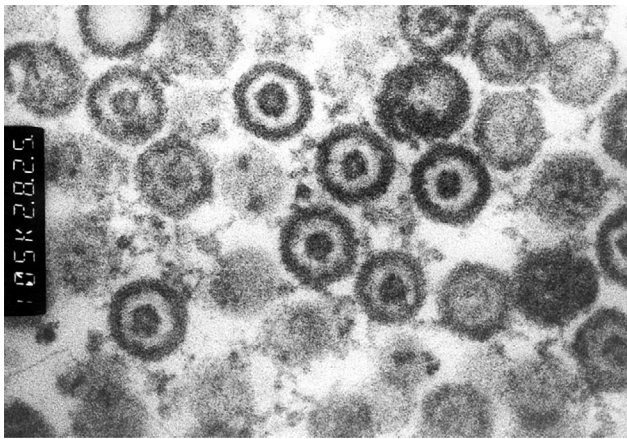


Figure 1 Electron micrograph of HSV-1 ($\times 105,000$) showing the composition of the virus: nucleocapsid with high density surrounded by the tegument with low density and the envelope with high density.

Note: Courtesy of the Institute of Virology and Antiviral Therapy, Jena University Hospital, Friedrich-Schiller University of Jena, Germany.

Abbreviation: HSV-1, herpes simplex virus type 1.

Epidemiology

Virus transmission and seroepidemiology

HSV-1 and HSV-2 are mainly transmitted by direct contact.⁶ The viruses are mostly acquired from symptomatic people with recurrent infections mainly at the lips or genitals or from asymptomatic persons shedding the virus through saliva and genitals.⁶ HSV-1 infections predominantly affect the body above the waist, and HSV-2 infections are dominant below the waist. After disappearance of protective maternal antibodies during the first year of life, the frequency of primary HSV-1 infections occurring mostly during infancy and childhood varies as a function of the socioeconomic status.⁷ Current seroprevalence data from Germany reveal an increase of anti-HSV-1 IgG from 19% by the age of 2–3 years, to 57% among 10- to 12-year-olds, to 69% by the age of 16–18 years, and to 78% among 28- to 30-year-olds.⁸ In European countries, HSV-1 seroprevalence varies in adults from 50% to $\geq 85\%$ during the last 2 decades.^{7,9}

HSV-2 is predominantly transmitted by sexual contact⁷ and has to be considered the major cause of genital herpes.¹⁰ Thus, the overwhelming majority of HSV-2 primary infection is acquired with starting sexual intercourse after puberty, and in contrast to HSV-1, HSV-2 infections are mainly diagnosed in adolescents and adults. As previously shown for Germany, HSV-2 seroprevalence increases from $\sim 3\%$ in children aged 10–15 years to 7% among 16- to 18-year-olds and to 14% among adults.⁸ Overall, HSV-2 seroprevalence rates depend on the age, sex, number of lifetime sexual partners, and socioeconomic status.^{7,9} Seroprevalences above the levels of the general population have been found in high-risk sexual

behaviors and HIV-positive people as well as in homosexual men.⁷ Several studies found significantly higher prevalence of anti-HSV-2 IgG among women than men.^{8,9,11,12} It has been discussed as a possible reason that men tend in principle to develop more asymptomatic genital HSV-2 infections than women, leading to higher rates of viral transmission from men to women.¹¹ By contrast, infected women have a higher proportion of symptomatic genital herpes promoting them to abstain from sexual intercourse. Because of the high antigenic cross-reactivity between HSV-1 and HSV-2, people with past primary HSV-1 infection probably have a lower risk of acquiring HSV-2 and vice versa.¹³ It is known that HSV-2 genital infections may increase the risk of acquiring HIV infection.¹⁴

Changes in seroepidemiology

During the past few decades, there have been changes especially in seroepidemiology of HSV-1. In the US, the overall HSV-1 seroprevalence decreased, in particular among children, between the 1980s and 2000s.¹⁵ In Germany, a reduced prevalence of HSV-1 antibody among children and adolescents has been found,⁸ and a substantial reduction of HSV-1 seroprevalence has recently been reported among Finnish children.¹⁶ The consequences may be a higher number of primary HSV-2 infections and/or a higher proportion of genital diseases caused by HSV-1 primary infections through oral sex among adolescents and adults. Indeed, there has been evidence that the number of genital herpes diseases due to HSV-1 primary infections has increased among young people, especially in the US.^{10,17} However, HSV-1 is less likely to lead to recurrences in the genital tract than HSV-2.¹⁸

Infection

HSV enters the body during primary infection through lesions of mucous membranes and skin and replicates locally in the keratinocytes of skin, epithelial cells of mucous membranes, and regional lymph nodes. It may follow a short viremia that is difficult to diagnose.¹⁹ After an incubation period of 2–12 days,²⁰ only 1% of infected people are at risk of developing diseases mostly characterized by typical herpes blisters at the site of virus entry, and the overwhelming majority, 99% of the infected people, show a clinically unapparent course.^{21,22} For HSV-2, the majority of primary infections are also asymptomatic.¹¹ After the onset of primary infection, both HSV-1 and HSV-2 migrate via retrograde axonal transport to sensory nerve ganglia where they establish latency, and the circular viral DNA persists in neurons.²³ The type of ganglia in which the viruses establish latency is dependent upon the ganglia associated with the

nerves innervating the site of infection. Thus, HSV-1 mostly remains latently in the trigeminal ganglion and HSV-2 in sacral ganglia. From there, viruses may be reactivated, and after neural anterograde transport, they may cause recurrent infections, especially of skin and mucous membranes.²² Recurrent infections, caused by HSV-1 or HSV-2 may occur in up to 40% of the latently infected individuals, but immunodeficient people are more frequently and especially more severely affected.²¹ Subclinical reactivations of HSV-1 or HSV-2 associated with asymptomatic shedding occur frequently^{24,25} and may help to boost the immune system. Clinically manifested recurrent infections caused by endogenous virus reactivation occur frequently after puberty in the case of immunogenetic predisposition, but their prevalence drops with age.²² It is known that virus reactivation can be triggered by multiple environmental and physiological factors such as fever, ultraviolet light, and trauma.^{26,27}

Even though there is extensive information on HSV biology, the absolute mechanism of HSV latency and endogenous virus reactivation is currently unknown. In human ganglia, HSV genomic DNA persists in a nonintegrated form, most likely as circular episome.²⁸ The latency-associated transcripts expressed by the virus seem to be of crucial significance for latency, since the most abundantly detected viral RNAs in latently infected ganglia originate from latency-associated transcripts and lytic regions are silent.²⁹ The HSV-1 reactivation has been hypothesized as a three-step epigenetically regulated process: 1) animation of latent virus genome by reactivation stimuli followed by generalized transcription of viral genes, 2) exit from latency with the classical three-step transcription of α , β , and γ genes, critically dependent on the function of HSV-1 VP1, and 3) production and release of infectious virus.³⁰

Genital herpes disease

Common diseases

An overview of different HSV-1 and HSV-2 diseases is given in Figure 2. The most common symptomatic HSV infections, irrespective of primary or recurrent infections, are localized on skin and mucous membranes such as herpetic gingivostomatitis (HSV-1), herpetic keratoconjunctivitis (HSV-1), herpes labialis or facialis (HSV-1), eczema herpeticum (HSV-1, rarely HSV-2), and herpes genitalis (HSV-2, rarely as a recurrent HSV-1 infection). In general, HSV has been considered the most common cause of sexually transmitted infections leading to ulcers.³¹ Genital disease caused by HSV-2 is clinically indistinguishable from that caused by HSV-1. Infections of the central nervous system (CNS) and

the sense organs may manifest as encephalitis, meningitis, myelitis, or retinitis (HSV-1, HSV-2), and in immunocompromised patients, disseminated infections with visceral manifestations of the lungs, liver, or esophagus (HSV-1, HSV-2) may occur. Additionally, neonatal or congenital (very rarely) herpes (HSV-2, HSV-1) results from perinatal or prenatal (intrauterine) infection among pregnant women or neonates.¹⁹

Primary genital herpes

Primary genital infections caused by HSV-1 or HSV-2 are mostly not associated with clinical symptoms and remain asymptomatic.³² In addition, atypical clinical presentations may occur. The classic clinical picture of primary genital herpes is characterized by typical lesions of mucous membranes appearing as maculae and papules, followed by vesicles, pustules, and ulcers. These lesions usually arise within 4–7 days after sexual exposure and last up to 3 weeks.³³ Lesions are mostly presented on the external genitalia characterized by bilateral clusters, but they can also be localized in the perianal region, on the buttocks, or upper thighs.³⁴ The typical patient's symptoms are pain, itching, burning, and dysuria. In primary infection, the genital lesions may be accompanied by lymphadenopathy, fever, cervicitis (women), and proctitis (homosexual men). The disease is often more severe in women than in men, also with regard to the prevalence of complications, including aseptic meningitis and urinary retention. Several authors differentiate between “initial primary” and “initial nonprimary” genital infection. While initial primary infection means the first virus exposure in anti-HSV-1/2 IgG-negative persons, initial nonprimary infection is defined as first HSV-1 or HSV-2 infection in persons having IgG antibodies against the other virus type than the one causing acute infection. Due to cross-reaction of HSV-1 and HSV-2 antibodies, initial nonprimary genital infections cause milder symptoms than initial primary infections.

Recurrent genital herpes and asymptomatic viral shedding

Reactivation of latent HSV can result in symptomatic recurrent episodes of genital herpes, called as recurrences, or in asymptomatic viral shedding. In general, almost all persons with symptomatic primary HSV-2 infection of the genital tract also have recurrences, and more than one-third have frequent recurrences.³⁵ By contrast, genital HSV-1 recurs infrequently. The genital HSV-1 recurrence rate is ~20% of the rate described for genital HSV-2 in the first year of

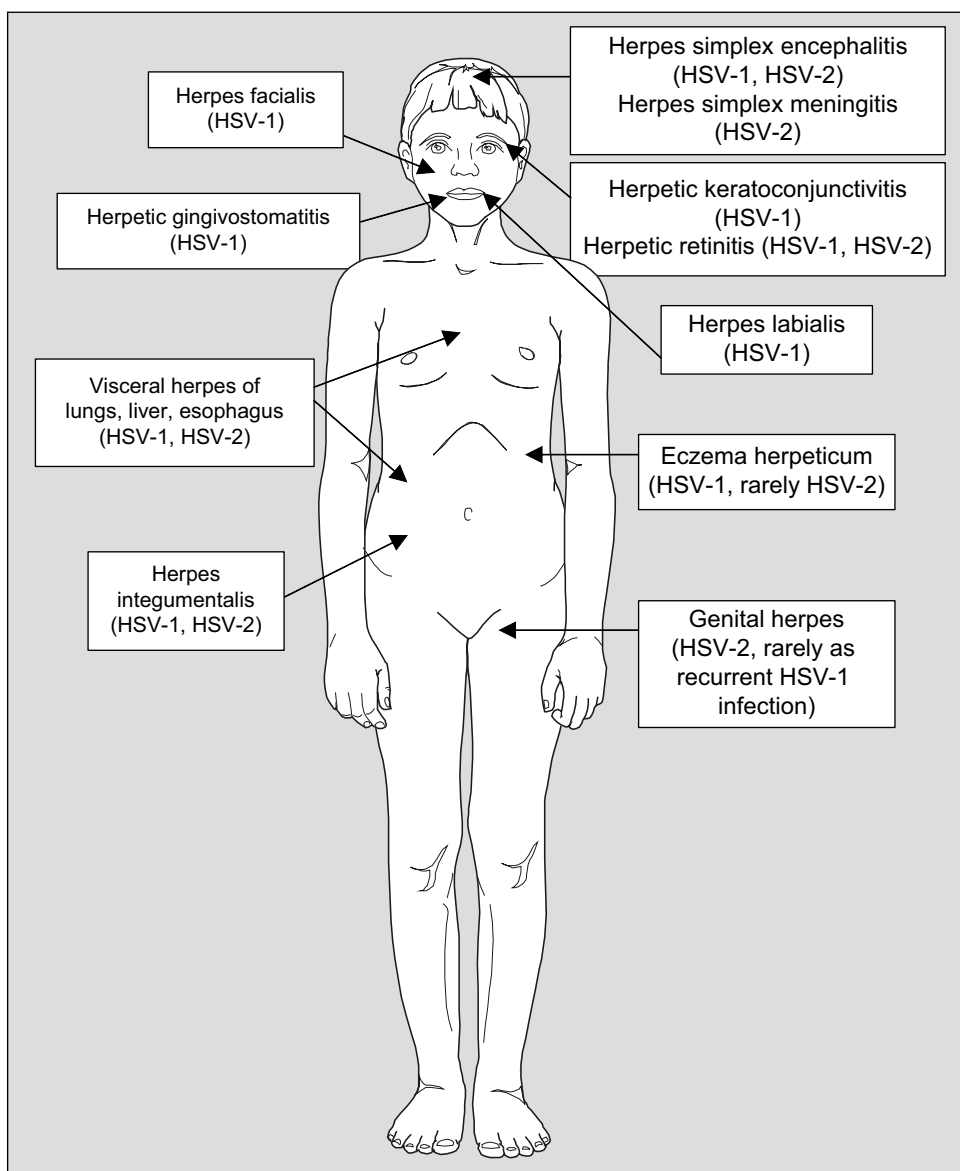


Figure 2 Different HSV-1 and HSV-2 diseases and their localization.

Abbreviations: HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2.

infection, and there is a considerably more rapid decrease over time for HSV-1 than for HSV-2.³⁶ As the earliest signs of recurrent episodes, prodromal symptoms may occur presenting as paresthesia and pains in the area of lumbosacral dermatomes.³⁴ In comparison to primary infection, recurrent genital herpes appears as a less severe disease with a shorter duration.³³ Usually, men have a small number of vesicles, and female infection is associated with genital lesions appearing as vesicles and ulcers or merely causes vulvar irritation lasting ~8–10 days.²⁰ A third of patients have been reported to have more than six recurrences per year.²⁰ According to experiences obtained from the consulting activities of the German Consulting Laboratory for Herpes Simplex Virus

and Varicella-Zoster Virus (Institute of Virology and Anti-viral Therapy, Jena University Hospital, Jena, Germany), especially young women, exposed to severe psychosocial stresses in work and family, are affected by recurrent genital herpes disease. It is important not to neglect that distinct recurrent genital herpes is often associated with significant psychosocial disturbances in the affected individuals and their sexual partners.³⁷

Asymptomatic genital shedding without clinical symptoms is most frequent in HSV-2-seropositive individuals. Studies have shown that nearly 90% of these persons have shedding episodes over time, while HSV-1 shedding has only been reported in rare cases.³⁸

Virus transmission

During genital herpes or asymptomatic viral shedding, HSV can be transmitted to sexual partners. Both primary and recurrent maternal infection during pregnancy can lead by intrauterine virus transmission to congenital disease, a rare disorder amounting to ~5% of all infections caused by HSV in neonates.³⁹ The danger of intrauterine viral transmission is highest after primary HSV-2 infection and during the first 20 gestational weeks. The fetal infection may result in abortion, stillbirth, or congenital disease, which is normally accompanied by skin lesions and eye and neurological damages.⁴⁰ Exposure to HSV in the genital tract at the time of delivery is regarded as the main reason of neonatal HSV infections, of which 70%–85% are caused by HSV-2.⁴¹ In the US, the incidence ranges from 5 to 31 per 100,000 live births, and the prognosis is poorer in neonatal HSV-2 infections than that related to HSV-1.³⁹ The highest risk of neonatal infection has been estimated in neonates born from mothers with primary HSV infection near term, but most neonatal infections arise from virus exposure through asymptomatic viral shedding via the genital tract near delivery.^{39,42} The clinical manifestations of neonatal HSV infections are categorized into three major groups of infections: (i) localized to skin, eye, and mucous membranes, (ii) CNS, and (iii) disseminated systemic.⁴³

Laboratory diagnosis

Virus detection

HSV-1 and HSV-2 can be detected in lesions of skin and mucous membranes in patients with acute genital herpes infections or in the absence of active lesions from genital mucous membranes to verify asymptomatic viral shedding. In the presence of mucocutaneous lesions, the collection of vesicular fluid by swabbing is the method of choice. The vesicle content or swab has to be placed into vials containing

physiological saline or viral transport medium. HSV-positive samples have to be shipped as dangerous goods category B and risk group 2 in accordance with the UN 3373 regulations.⁴⁴ The patient's sample within a primary container has to be placed within an outer packaging containing adsorbing material, and the transportation should be carried out in a cardboard box. Shipment is recommended at room temperature unless samples have to be used for isolation of HSV in cell culture.⁴⁴ In this case, cooling is required, since the infectivity of HSV is highly dependent on temperature, humidity, and pH value.⁴⁵

Acute genital HSV infections are diagnosed (Table 1) by laboratory detection of DNA of HSV-1 and HSV-2 by means of polymerase chain reaction (PCR).⁴⁶ In case of complications or the involvement of other organs, cerebrospinal fluid, tissue, bronchoalveolar lavage, ethylenediaminetetraacetic acid blood, serum, amniotic fluid, or intraocular fluid can be used as specimens. The PCR method should be used to discriminate between both HSV-1 and HSV-2.⁴⁷ Many laboratories use qualitative or quantitative in-house PCR assays, but commercial test kits are also available.⁴⁵ Alternatively, the acute genital HSV infection or asymptomatic shedding can be diagnosed by viral isolation in cell culture. It is appropriate to type the virus isolates by means of immunofluorescence using HSV serotype-specific fluorescein-labeled monoclonal antibodies. 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 in many cell types such as human embryonic fibroblasts, Vero, or HEp-2 cells. However, because of the higher sensitivity,⁴⁸ the PCR technique is currently accepted as gold standard in many laboratories. Recently, the Centers for Disease Control and Prevention stated that the “specific evaluation of genital, anal, or perianal ulcers includes culture or PCR testing for genital herpes”.⁴⁹ Furthermore, the direct detection of HSV antigens

Table 1 Methods for detection of HSV including viral nucleic acid (DNA)

Principle	Method	Patient samples	Remarks
Detection of viral DNA	Polymerase chain reaction	Vesicle content/swab, in 1 mL physiological saline or viral transport medium Cerebrospinal fluid, tissue, bronchoalveolar lavage, EDTA blood, amniotic fluid, intraocular fluid	Basic diagnostics
Viral isolation	Viral growth in cell culture, detection by monoclonal antibody	Vesicle content in viral transport medium with special swab, tissue, bronchoalveolar lavage Transport under cooling (2°C–8°C)	Special diagnostics
Virus detection	Immunofluorescence test using monoclonal antibody	Cell-rich vesicle content in viral transport medium with special swab, tissue	Basic diagnostics Reduced sensitivity and specificity
Virus typing	Immunofluorescence test using monoclonal antibody	Virus isolate	Basic diagnostics

Abbreviations: HSV, herpes simplex virus; EDTA, ethylenediaminetetraacetic acid.

by means of commercial detection systems on the basis of immunofluorescence or enzyme-linked immunosorbent assay (ELISA) is a frequently used and cost-effective assay. This technique provides results within a few hours, but it lacks sensitivity and specificity.^{31,50} It has to be taken into account that laboratory methods, which diagnose HSV-1 or HSV-2 infection 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 widely used for the indirect laboratory diagnosis of infections caused by HSV-1 or HSV-2. Serological methods (Table 2) 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 by the use of HSV type-specific antibody assays. Because of the close relationship between HSV-1 and HSV-2, the determination of type-specific IgG is only possible by the use of ELISA or immunoblot on the basis of glycoproteins G (gG-1) or C (gC-1) of HSV-1 and the glycoprotein G (gG-2) of HSV-2.^{4,5} For the interpretation of results, one has to bear in mind that there is a partial cross-immunity between HSV-1 and HSV-2. HSV type-specific IgG assays are potentially useful

to identify HSV carriers, in particular of HSV-2.^{51,52} The presence of anti-HSV-2 IgG implies most likely anogenital infection and high probability of asymptomatic viral shedding. HSV type-specific serological tests have been available commercially for >1 decade, and there is a strong consensus that assays on the basis of gG-1 and gG-2 are most accurate for discrimination of past (latent) HSV-1 from past (latent) HSV-2 infection. It should be, however, considered that the specificity can be reduced in populations with a high prevalence of diseases caused by HIV.⁵³ If a first 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 of anti-HSV-1 and anti-HSV-2 IgG may permit a distinction between primary and recurrent HSV-1 or HSV-2 infection.⁵⁴ That means, for example, when HSV-2 is detected in genital lesions of pregnant women some weeks before delivery, 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. Despite the advantages of HSV type-specific serology, many laboratories do not offer these assays but provide only type-common serologic tests.^{55,56} Table 3 provides a summary of virological and serological data for the laboratory diagnosis of HSV infection with and without genital herpes lesions and asymptomatic viral shedding.

Determination of anti-HSV-1 or anti-HSV-2 IgG avidity may also allow the differentiation between primary and recurrent HSV-1 or HSV-2 infections, but there is only very limited experience in this including the diagnosis of genital herpes.⁵⁷ Intrathecal HSV antibodies may be of value for the retrospective laboratory diagnosis of CNS infections caused by HSV.⁵⁸ Anti-HSV IgM is only of minor significance for the early diagnosis of acute HSV infection. Due to cross-reactions to other herpesviruses, especially the varicella-zoster virus, IgM assays may show false-positive results. Only type-common HSV IgM ELISAs with high sensitivity and specificity may be useful to confirm acute HSV infections.⁵⁹ This can apply to IgM as a marker for newly acquired genital HSV infections especially caused by HSV-2⁶⁰ and may be of significance in particular in the management of pregnant women. However, IgM results appear to be ineffective at discriminating early (primary) from established infections,⁶¹ and the positive predictive value of HSV IgM assays for acute HSV infection is low. A further drawback is that the determination of IgM antibodies has practically no significance for the timely diagnosis of acute primary and recurrent HSV infection. The use of HSV type-specific IgM ELISAs, which are offered

Table 2 Different methods used for detection of HSV-specific antibodies

Method	Remarks
Ligand assays (ELISA, chemiluminescence immune assay, etc)	Determination and differentiation of immunoglobulin (Ig) classes (IgG, IgM) in serum, plasma, and cerebrospinal fluid Determination of type-specific antibodies to viral glycoproteins (gG-1, gC-1, gG-2) Determination of type-common antibodies using whole viral antigen from cell cultures infected with HSV-1 or HSV-2 Simple handling, distributed commercially, automated, basic diagnostics
Indirect fluorescence antibody test	Determination and differentiation of Ig classes (IgG, IgM) in serum, plasma, and cerebrospinal fluid Simple handling, distributed commercially, requires experience in microscopic evaluation, special diagnostics
Immunoblot	Qualitative determination of type-specific IgG antibodies to viral glycoproteins (gG1, gG2) in serum Simple handling, sensitive, distributed commercially, automated performance and analysis, special diagnostics
Neutralization assay	Detection of HSV-1- and HSV-2-neutralizing antibodies in serum, difficult, special diagnostics

Abbreviations: HSV, herpes simplex virus; ELISA, enzyme-linked immunosorbent assay; HSV-1, HSV type 1; HSV-2, HSV type 2.

Table 3 Laboratory data for diagnosis of HSV infection dependent on genital herpes lesions

Clinical signs	HSV serology			PCR		Interpretation/status of infection
	HSV-1/2 IgG	HSV-1 IgG	HSV-2 IgG	HSV-1	HSV-2	
Primary genital herpes	Neg	Neg	Neg	Pos	Neg	Acute HSV-1 infection
	Pos	Neg	Pos	Pos	Neg	Acute HSV-1 infection, HSV-2 latency
	Neg	Neg	Neg	Neg	Pos	Acute HSV-2 infection
	Pos	Pos	Neg	Neg	Pos	Acute HSV-2 infection, HSV-1 latency
Recurrent genital herpes	Pos	Pos	Neg	Pos	Neg	Recurrent HSV-1 infection
	Pos	Pos	Pos	Pos	Neg	Recurrent HSV-1 infection, HSV-2 latency
	Pos	Neg	Pos	Neg	Pos	Recurrent HSV-2 infection
	Pos	Pos	Pos	Neg	Pos	Recurrent HSV-2 infection, HSV-1 latency
No genital herpes lesions	Neg	Neg	Neg	Neg	Neg	Susceptibility
	Pos	Pos	Neg	Neg	Neg	Past HSV-1 infection (HSV-1 latency)
	Pos	Neg	Pos	Neg	Neg	Past HSV-2 infection (HSV-2 latency)
	Pos	Pos	Pos	Neg	Neg	Past HSV-1 and HSV-2 infection (HSV-1 and HSV-2 latency)
	Pos	Pos	Neg	Pos	Neg	Asymptomatic shedding of HSV-1, past HSV-1 infection (HSV-1 latency)
	Pos	Neg	Pos	Neg	Pos	Asymptomatic shedding of HSV-2, past HSV-2 infection (HSV-2 latency)
	Pos	Pos	Pos	Pos	Neg	Asymptomatic shedding of HSV-1, past HSV-1 and HSV-2 infection (HSV-1 and HSV-2 latency)
	Pos	Pos	Pos	Neg	Pos	Asymptomatic shedding of HSV-2, past HSV-1 and HSV-2 infection (HSV-1 and HSV-2 latency)

Abbreviations: HSV, herpes simplex virus; PCR, polymerase chain reaction; HSV-1, HSV type 1; HSV-2, HSV type 2; Neg, negative; Pos, positive.

with increasing frequency, is practically superfluous, since the sensitivity and/or specificity can significantly be reduced.⁵⁹ In conclusion, clinical decisions for antiviral therapy of HSV infections should principally not be taken on the basis of HSV IgM serologic results alone.

Antiviral treatment

Standard antiviral therapy

Acyclovir, valacyclovir, and famciclovir are available for standard antiviral treatment of genital herpes (Table 4). All drugs are acyclic nucleoside analogs,⁶³ and their specific antiviral activity is based on one key enzyme of HSV-1 and HSV-2, the thymidine kinase, that converts the antiviral compounds to their monophosphates. Catalyzed by cellular enzymes, the monophosphates of nucleoside analogs are further phosphorylated to diphosphates and the active triphosphates that inhibit and fix the viral DNA polymerases, an essential enzyme for HSV-1 and HSV-2 replication. The triphosphates may also be incorporated into the growing DNA chain as “false” substrate, leading to an inhibition of viral DNA synthesis. In the case of acyclovir/valacyclovir, this is caused by the absence of the hydroxy group in 3' position essential for further linking. Other nucleoside analogs such as penciclovir arising from famciclovir can be incorporated into the growing DNA chain.

Acyclovir⁶³ is used as first-line antiviral drug for the treatment of HSV infections including genital herpes. However,

a disadvantage is that acyclovir has a low oral bioavailability of ~15%–30%. Diseases of skin and mucous membranes in immunocompetent persons, which also includes genital herpes, are treated with oral acyclovir, but during severe HSV infections, in particular among immunocompromised patients, the drug has to be used intravenously (iv). In genital herpes, the dosage depends on the status of infection, immunocompetency, and pregnancy. If there are more than four to five recurrences of genital herpes per year, a suppressive antiviral therapy may be considered.^{62,64} Data from different randomized clinical trials⁶⁵ and Cochrane review⁶⁶ have shown especially the efficacy of acyclovir during pregnancy in suppression of genital herpes. The topical use of acyclovir is only recommended for the treatment of labial herpes or herpetic keratoconjunctivitis and exclusively in mild cases of genital herpes (Table 4). Acyclovir is not officially licensed for the antiviral therapy during pregnancy, and administration should be especially avoided in pregnant women before the end of the 14th gestational week.⁴⁴ However, results from the manufacturer's pregnancy registries⁶⁷ and a Danish population-based retrospective cohort study⁶⁸ have not shown an increased rate of major birth defects after oral administration of acyclovir and its topical use. Nevertheless, patients should be informed about the limited data, especially during early pregnancy, and consent should be obtained before the drug is used. Following topical application, systemic absorption of acyclovir is minimal.⁶⁹ The iv administration

Table 4 Antiviral treatment of genital herpes

Disease/kind of therapy	Acyclovir	Valacyclovir	Famciclovir
Primary genital herpes	3× 400 mg orally per day for 7–10 days 5× 200 mg orally per day for 7–10 days	2× 500 mg orally per day for 7–10 days	3× 250 mg orally per day for 7–10 days
Severe cases of primary genital herpes	3× 5 mg/kg body weight intravenously for 5–7 days, under immunosuppression for 10 days		
Primary genital herpes in pregnant women ^a	5× 200 mg orally per day for 10 days		
Recurrent genital herpes (<5 recurrences per year) ^b	2× 800 mg orally for 5 days 3× 400 mg orally for 5 days 3× 800 mg orally for 2 days	2× 500 mg orally for 3 days 1× 1,000 mg orally for 5 days	2× 125 mg orally for 5 days 2× 1,000 mg orally for 1 day
Recurrent genital herpes in pregnant women	3× 400 mg orally from 36th gestational week until delivery	2× 250 mg orally for 3 days from 36th gestational week until delivery	
Preventive therapy before delivery	2× 400 mg orally for maximally 6 months		
Suppressive therapy (≥5 recurrences per year)	2× 400 mg orally for maximally 6 months 4× 200 mg orally for maximally 6 months	1× 500 mg orally for maximally 6 months	2× 250 mg orally for maximally 6 months

Notes: ^aAcyclovir is not approved during pregnancy (off-label use). Administration should be especially avoided before the end of 14th gestational week. ^bIn mild cases, acyclovir or foscarnet sodium may be administered topically, but this is not sufficient especially during pregnancy. For more information, see Gupta et al,³⁴ Centers for Disease Control and Prevention⁵¹ and German STI-Society.⁶²

of acyclovir is occasionally accompanied by side effects of the CNS, and oral administration of acyclovir can lead to gastrointestinal symptoms. Combining acyclovir with drugs toxic to the kidney should be avoided. If acyclovir is used iv, the laboratory parameters of kidney and liver metabolisms should be monitored.

Valacyclovir,⁶³ an L-valyl ester prodrug of acyclovir, is administered orally. The drug is converted into acyclovir, catalyzed by the hepatic valacyclovir hydrolase. Since the oral bioavailability of valacyclovir is 54%, the considerably higher acyclovir concentrations than after the oral use of acyclovir result in longer dosing intervals and a higher compliance of valacyclovir. Valacyclovir is used as first-line antiviral drug for the therapy of genital herpes in immunocompetent adults. Comparable to acyclovir, data support the efficacy of valacyclovir during pregnancy in the suppression of recurrent genital herpes.^{65,66} Valacyclovir is not approved for antiviral treatment in children and adolescents, since safety and effectiveness have not been established especially in children <12 years of age.⁷⁰ Valacyclovir is also not licensed for use in pregnant women. Although available data are reassuring as to the safety of valacyclovir during pregnancy,⁶⁸ there is substantially less experience than with acyclovir. Side effects after the use of valacyclovir correspond widely to those after oral administration of acyclovir.

Famciclovir⁶³ is the inactive double diacetyl precursor of the acyclic nucleoside analog penciclovir, a highly active anti-herpesvirus agent, deriving from ganciclovir. Penciclovir has

a very low oral bioavailability and can only be used for topical antiviral therapy of local HSV infections, but it arises after oral administration of famciclovir by the separation of ester groups in the gastrointestinal tract. The oral bioavailability of famciclovir is calculated as 77%. It has also been accepted as first-line option for antiviral therapy of genital herpes. The higher stability of triphosphate of penciclovir compared to that of acyclovir might result in a prolonged antiviral efficacy.⁷¹ Similar to valacyclovir, famciclovir is not licensed for use in children and adolescents, immunosuppressed patients under the age of 25 years, and in pregnant women. There is quite limited information on the safety of famciclovir during pregnancy. Thus, it should not be considered the medication of choice for antiviral therapy of HSV infections in pregnant women.⁷² The most common side effects of famciclovir are headache, nausea, and mental confusion.

Other antiviral therapeutic options

Especially in immunocompromised patients, genital herpes can be related to resistance to acyclovir/valacyclovir and cross-resistance to famciclovir after prolonged antiviral treatment. The prevalence of acyclovir-resistant HSV-2 strains has been reported in up to 5% of HIV-positive patients.^{73,74} In these cases, the pyrophosphate analog foscarnet (triso-dium phosphonoformate) is recommended for alternative antiviral treatment at a dose of 3× 40 (–80) mg/kg body weight iv until clinical resolution.⁵¹ Additionally, suspected resistance should be verified by genotypic and/or phenotypic

resistance testing. Foscarnet is known to inhibit the essential DNA polymerases of several DNA as well as RNA viruses and does not have to be metabolized for the expression of antiviral activity by the prevention of the pyrophosphate exchange. Therefore, it is also active against acyclovir-/valacyclovir-/famciclovir-resistant HSV strains. Because of the high cytotoxicity, foscarnet is known to induce significant side effects such as abnormalities in the function of liver and ulcers of the urogenital mucous membranes. Since the antiviral therapy with foscarnet has to be carried out under inpatient conditions, the administration of the nucleotide analog cidofovir (off-label use, 5 mg/kg body weight once weekly or later every 2 weeks iv until clinical resolution),⁷⁵ licensed for the antiviral therapy of cytomegalovirus retinitis in patients with AIDS, may be a further option. The topical use of 1% foscarnet cream or 1% cidofovir gel has been described to lead to significant healing of genital herpes in HIV-positive people with acyclovir-resistant HSV.⁷⁵

In future, novel antiviral drugs belonging to the so-called helicase–primase inhibitors may improve significantly the antiviral treatment of genital herpes. It has been assumed that these non-nucleosidic inhibitors bind to the helicase–primase complex, that is essential for virus replication, and inhibit the viral DNA synthesis. Several orally administered drugs have promising anti-HSV activity as well as preclinical profiles of safety and pharmacokinetics. Amenamevir (ASP2151) has been demonstrated to be safe and effective in treating genital herpetic lesions in animal studies and clinical trials.⁷⁶ In Phase II trials, the drug pritelivir (BAY 57-1293, AIC316) showed a significant effect in reducing asymptomatic genital shedding of HSV-2 as well as the herpetic lesions in individuals with genital herpes.⁷⁷ Both drugs seem to be potentially useful for the treatment of infections caused by acyclovir-resistant HSV-1 and HSV-2 strains without significant side effects.⁷⁸

The use of microbicides formulated in various delivery systems, for example, gels, creams, or lotions, may help to prevent sexually transmitted diseases such as genital herpes caused by transmission during sexual activities. The best investigated drug is tenofovir, a nucleoside analog reverse transcriptase inhibitor that is primarily used to prevent and treat the HIV infection. Recently, it has been shown that the vaginal application of tenofovir gel 12 hours before sexual intercourse reduces the acquisition of HSV-2 among HSV-2-negative women.⁷⁹ Further studies in women with symptomatic genital HSV-2 infection revealed that neither oral nor vaginal administration of tenofovir results in substantial decrease of viral shedding or symptomatic lesions.⁸⁰ It was concluded from these studies that periodical intravaginal

application of tenofovir gel does not have the potential as a first-line option for HSV prevention, but it can increase the range of options for the prevention of genital herpes. A further promising candidate of microbicides effective against HSV after vaginal application is VivaGel™ that is, however, not yet commercially available. For the active ingredient SPL7013, a dendrimer produced by nanotechnology, anti-HIV and anti-HSV activity has been shown *in vitro*, in animal models, and in Phase I clinical trials among women.^{81,82}

Resistance testing

An antiviral treatment failure caused by resistance to acyclovir, valacyclovir, or famciclovir can most likely be presumed in the absence of clinical improvements after the application of antiviral medication for at least 10 days.⁸³ This means that it is a clinical treatment failure to give rise to resistant HSV strains. Therefore, phenotypic and/or genotypic resistance testing should be carried out. Could any resistance to acyclovir/valacyclovir, almost always combined with cross-resistance to famciclovir, be confirmed, an alternative antiviral therapy using foscarnet is recommended. Since especially the testing of resistance phenotype is time-consuming and requires at least 7–10 days, one should not wait for the laboratory results when the clinical resistance is pronounced.

For phenotypic resistance testing, plaque reduction or cytopathic effect inhibition assays, dye uptake methods, and DNA hybridization tests have mainly been described.⁸⁴ The plaque reduction or cytopathic effect inhibition assays have been used most frequently. Susceptibility of HSV isolates to antiviral drugs can be assessed on the basis of virus-specific morphological cell changes, the so-called cytopathic changes. It is possible to facilitate and objectify the test evaluation by means of cell proliferation assays such as the tetrazolium reduction test.⁸⁵ Using these assays, the amount of living cells and the concentrations of antiviral drugs inducing 50% inhibition of viral replication can be estimated spectrophotometrically. Due to the use of different cell cultures, there is no international standardization of the cutoff value for any resistance to date. Therefore, it is necessary that susceptible HSV-1 or HSV-2 reference strains have to be included into each test approach as sensitive controls. It is an established practice to consider HSV isolates as resistant to acyclovir (valacyclovir), penciclovir (famciclovir), and cidofovir if the 50% effective/inhibitory concentration is three to five times higher than that of the susceptible reference strain.^{86,87} To assess a rarely observed resistance to foscarnet, the corresponding values should be estimated >330 μM.⁸⁸ Since phenotypic resistance testing allows a clear interpretation

of results, this method has been accepted as gold standard for HSV resistance testing till now. However, the methods require a high expenditure of time and material, and they are currently not standardized. In the laboratory, resistance phenotype can only be tested if there is a high amount of viable virus obtained from vesicle fluids or mucocutaneous swabs and grown in cell culture.

For genotyping resistance testing of HSV, the viral thymidine kinase and DNA polymerase genes are amplified and sequenced.⁸⁴ To identify nonsynonymous mutations, sequence data must be interpreted in comparison to the published sequences of susceptible reference strains provided in the GenBank (eg, HSV-1 strain 17 accession no X14112 and HSV-2 strain HG 52 accession no Z86099.2). The PCR with modified primers has been used occasionally for rapid identification of special well-known mutations. Frameshift mutations, additional stop codons, as well as well-known nonsynonymous nucleotide substitutions in particular within conserved or active gene regions can be interpreted with a very high level of probability as related to resistance. The interpretation of amino acid substitutions outside of conserved or functionally essential gene centers requires the access to databases in which all mutations within the thymidine kinase and DNA polymerase genes well known from the literature are described.⁸⁴ Till now, the most reliable method to assess the significance of nonsynonymous mutations for resistance of HSV-1 and HSV-2 is the alignment of the resistance phenotype and genotype of viable virus strains. For analysis of resistance genotype, a limiting effect may have the restricted amount of viral DNA, if no viable virus strains are available. In addition, the interpretation of sequence data may be difficult when mixtures of viral mutants and wild-type strains are detected in patient samples.⁸⁹ However, a crucial advantage of genotyping is a significantly shorter duration (~2 days depending on the viral load) compared to phenotyping and possibility to test samples without the need to grow the virus in cell culture which is of significant clinical relevance for the antiviral therapeutic decision.

Prevention

Common procedures

For counseling couples, HSV type-specific serology is a useful tool to identify HSV-2 carriers who can transmit the virus to their sexual partner. If the partner of HSV-2-positive persons has no detectable antibody, the use of condoms for safer sex should be recommended.⁹⁰ In case of symptomatic genital herpes lesions or prodromal symptoms, people should be counseled to abstain from sexual intercourse.⁹¹

Both partners should be informed about their HSV status and the possible consequences of genital herpes as well as asymptomatic shedding including the impact on pregnancy. Especially in young women with high physical and mental stresses, psychotherapeutic support can help to reduce the frequency of recurrent genital episodes.

Vaccination

Despite any attempts, neither therapeutic nor prophylactic vaccines are currently available for treatment and prevention of genital herpes. The primary goal of therapeutic vaccines is to reduce HSV recurrences and asymptomatic shedding in patients with existing latent HSV infection. By contrast, prophylactic vaccines aim at prevention of acute disease and latent infection in HSV-seronegative people. To date, many therapeutic and prophylactic vaccine candidates have been tested especially in mouse and guinea pig vaginal infection models.⁹² However, the animal models have several disadvantages, and the results can only be transferred partially to humans. Nevertheless, promising results have been obtained by combination of the CD8⁺ T-cell immunogen ICP4 with the HSV-2 gD to induce potent humoral and cellular immune responses.⁹³ Recently, a novel adjuvanted HSV-2 subunit vaccine consisting of the recombinantly expressed viral proteins gD2, UL19, and UL25 has been tested successfully in animal models as a promising vaccine candidate for the treatment and prevention of genital herpes by vaccination.⁹⁴

In humans, a therapeutic vaccine has to induce immune response that is more effective than those after recurrent HSV infection. Different results were achieved in randomized, placebo-controlled clinical trials in men and women with more than four recurrences of genital herpes per year using gD2 and combined gB2/gD2 HSV-2 subunit vaccines with MPL–alum or MF59 adjuvants.^{95,96} While the use of gD2 with MLP and alum led to fewer virologically confirmed HSV-2 recurrences,⁹⁵ gB2/gD2 plus MF59 only resulted in a reduced severity of symptoms, time of healing, and duration to develop new lesions but not in a reduction of recurrences.⁹⁶ Similarly, modified live attenuated deletion mutant viruses have been evaluated with varying degrees of success in randomized placebo-controlled studies.^{97,98} Using a live attenuated HSV-2 with a deletion within the large subunit of ribonucleotide reductase to compromise the ability to establish viral latency, recurrent HSV-2 genital diseases were prevented in one-third of 32 patients of both sexes with a minimum of five recurrences per year initially.⁹⁷ In the second study, the use of a replication-incompetent HSV-2 vaccine lacking the glycoprotein H gene had no efficacy on

the number of HSV-2 recurrences and genital virus shedding in men and women.⁹⁸ Clinical trials for prophylactic HSV-2 vaccines have included gD2/gB2 subunit vaccines with MF-59 adjuvant as well as gD2 subunit vaccines with MLP–alum adjuvant. While the gD2/gB2 subunit vaccine did not induce any seroconversion in HSV-2-negative partners,^{99,100} different studies using gD2 subunit vaccines showed (i) efficacy in HSV-1- and HSV-2-seronegative women but not in HSV-1-seropositive women and men¹⁰¹ and (ii) efficacy against genital infection caused by HSV-1 but not HSV-2 in HSV-1- and HSV-2-seronegative women.¹⁰² Even though there is currently no licensed therapeutic or prophylactic vaccine against genital herpes in humans, preliminary studies have provided promising insights into mechanisms for treatment and prevention of genital herpes by vaccination. Virus-specific antibodies are most likely the dominant mediators to protect against primary infection, while cellular immunity probably triggers the prevention of recurrences.^{92,103}

Conclusion

The genital herpes is a global medical problem, and the medical management of affected patients is often unsatisfactory. Considering the present possibilities of laboratory diagnosis, antiviral therapy, and prevention by suppressive antiviral treatment, the management of patients including their counseling may significantly be improved. Nevertheless, further effective and well-tolerated drugs for antiviral treatment, especially in case of acyclovir resistance, are required, and even more vaccines must be provided for the effective prevention of primary and recurrent genital herpes infections. To date, the data about the use of the novel helicase–primase inhibitors as well as prophylactic and therapeutic HSV vaccines have provided promising results.

Disclosure

The author reports no conflicts of interest in this work.

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