Herpes Genitalis: Diagnosis, Treatment and Prevention

Diagnostik des Herpes genitalis, einschließlich antivraler Therapie und prophylaktischer Möglichkeiten

Author

A. Sauerbrei

Affiliation

Institut für Virologie und Antivirale Therapie, Konsiliarlabor für HSV und VZV, Universitätsklinikum Jena, Jena, Germany

Key words

- herpes simplex virus
- herpes genitalis
- laboratory diagnostics
- antiviral therapy
- prophylaxis

Schlüsselwörter

- Herpes-simplex-Virus
- Herpes genitalis
- Labordiagnostik
- antivirale Therapie
- Prophylaxe

Abstract

Herpes genitalis is caused by the herpes simplex virus type 1 or type 2 and can manifest as primary or recurrent infection. It is one of the most common sexually transmitted infections and due to associated physical and psychological morbidity it constitutes a considerable, often underestimated medical problem. In addition to providing the reader with basic knowledge of the pathogen and clinical presentation of herpes genitalis, this review article discusses important aspects of the laboratory diagnostics, antiviral therapy and prophylaxis. The article is aimed at all health-care workers managing patients with herpes genitalis and attempts to improve the often suboptimal counselling, targeted use of laboratory diagnostics, treatment and preventive measures provided to patients.

Introduction

Herpes genitalis is among the most common sexually transmitted infections. It is caused by the herpes simplex virus type 2 (HSV-2) and also, increasingly, the herpes simplex virus type 1 (HSV-1). Both organisms are enveloped DNA viruses that are sensitive to disinfectants and environmental factors [1]. Due to marked genetic homology between HSV-1 and HSV-2 numerous biological similarities and antigenic cross-reactions between the viruses exist. Type-specific epitopes include the viral glycoproteins (g) gG (HSV-1 and HSV-2) and gC (HSV-1) [2,3].

The primary mode of transmission of both HSV-1 and HSV-2 is through direct contact. Initial infection with HSV-1 occurs most often during childhood following the disappearance of maternal antibodies during the first year of life. Current data on seroprevalence in Germany show a rise in anti-HSV-1 IgG to approx. 20% by the age of 2–3 years, to 57% in 10–12-year-olds, approx. 70% in 16–18-year olds and around 80% in adults aged 28–30 years [4]. From the age of 40 years and onwards one can assume an HSV-1 seroprevalence of ≥ 85–90% [5]. Since HSV-2 is mainly transmitted through sexual intercourse infection rates only rise after puberty. In Germany the prevalence of anti-HSV-2 IgG antibodies rises from approx. 3% in 10–15-year-olds to 7% in the age group 16–18 years, to approx. 14% in adults [4]. Higher seroprevalences are found internationally among people who regularly change sexual partners and among homosexual men [6]. Numerous studies have shown a significantly higher HSV-2 seroprevalence in women than in men [4,5]. As a possible

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Correspondence

Prof. Dr. Andreas Sauerbrei
Institut für Virologie und Antivirale Therapie
Konsiliarlabor für HSV und VZV
Universitätsklinikum Jena
Hans-Knöll-Straße 2
07745 Jena
Germany
Andreas.Sauerbrei@med.uni-jena.de

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reason for this it has been suggested that men have asymptomatic genital HSV-2 infections more often than women, resulting in higher virus transmission rates from men to women [7]. Partial clinical cross-immunity exists between HSV-1 and HSV-2 and as a result, primary genital HSV-2 infection may be asymptomatic in patients with HSV-1 immunity and vice versa. A reduced HSV-1 seroprevalence among young people (adolescents) and adults may be associated with higher numbers of primary HSV-2 or HSV-1 infections due to oral sex. There is published evidence of this in the USA [8, 9] but not yet in Germany. Genital HSV-2 infection is associated with an increased risk of HIV infection [10].

**Asymptomatic genital viral shedding**

In the majority of cases endogenous viral reactivation is characterised by asymptomatic genital viral shedding. Most commonly HSV-2 is shed by HSV-2 seropositive patients, and this is the case for almost anyone who is anti-HSV-2 IgG positive [21]. In contrast, HSV-1 shedding is uncommon. These data allow the assumption, with a high level of certainty, that HSV-2 seropositive people should always be regarded as potential virus excretors.

**Virus transmission**

People with clinically manifest/apparent herpes genitalis and people who shed HSV asymptptomatically can transmit the virus to their sexual partners. This almost always occurs via direct contact during sexual intercourse. In recent years an increased incidence of primary genital HSV-1 infection has been reported in the USA, particularly among adolescence and young adults [8, 9]. This can most probably be ascribed to oral sex, which is more commonly practiced in this age group. Due to its low environmental stability HSV can only remain infectious for a period of days on moist surfaces [22]. It can therefore be assumed with a high level of certainty that when normal hygiene (including bodily hygiene) is maintained, modes of transmission other than sexual intercourse do not play a significant role. Intrauterine and perinatal viral transmission are the exceptions. Both primary and recurrent HSV infection in pregnant women can result in intrauterine viral transmission and congenital HSV infection, although the incidence is low at just 5% of all HSV infections in newborns [23]. The clinical consequences of fetal infection described include abortion, stillbirth or other congenital manifestations usually including skin and eye lesions and/or neurological symptoms [24]. The highest risk of fetal infection is during the first 20 weeks of pregnancy, and with primary maternal HSV-2 infection. Viral transmission to the child via the mother’s genital tract during labour is regarded as the most common cause of neonatal HSV infection; of these infections 70–85% are caused by HSV-2 [25]. The incidence in the USA is quoted at 5 to 31 per 100000 live births with a worse prognosis for HSV-2 infection compared to HSV-1 [23]. There are no data available on the incidence of neonatal HSV infection in Germany. The highest risk is with perinatal maternal primary HSV infection, however most neonatal infections occur around the birth in the presence of asymptomatic genital tract viral shedding [23, 26]. Disease manifests as localised infection of the skin, eyes and mucous membranes, CNS infection or disseminated systemic infection [27].

**Laboratory Diagnostics**

**Sample submission**

Herpes simplex virus-containing samples must be transported as UN 3373 category B, hazardous substances [22]. The primary vessel containing the patient sample must be sent in a covering tube within a labelled transport container (cardboard box) with adsorbing material. In general samples can be sent at room temperature unless the material is being sent for virus isolation, in which case cooling is recommended.

**Virus detection**

The laboratory diagnosis of acute genital HSV infection or asymptomatic virus shedding is made via direct viral detection (Table 1). The method of choice is demonstration of viral genomes in skin or mucous membrane swabs using the polymerase chain re-
The detection of virus-specific antibodies for confirming HSV infection is widely used in clinical practice. One should however be aware of the limited value of serology results. HSV serology is mainly useful for confirming seroconversion following primary infection, through demonstration of IgG. This can be of particular value in the diagnosis of HSV-2 infections in the context of antenatal care. Confirming seroconversion is also possible by demonstrating type-specific IgG antibodies, and since HSV-1 and HSV-2 are so closely related this is only possible using ELISA/immunoblot on the basis of HSV-1 gG-1 or gC-1, and HSV-2 gG-2 [2,3]. When interpreting results it is important to consider that partial cross-immunity exists between HSV-1 and HSV-2. The importance of HSV type-specific IgG is mostly that it allows rapid, reliable and economical identification of HSV-2 carriers and potential virus shedders [31,36]. Thus a patient in whom anti-HSV-2 IgG is detected can be considered a potential virus shedder and transmitter who may also suffer from anogenital HSV infection. If an initial serum sample is available from the early stage of a herpes genitalis infection, primary and recurrent infections can be differentiated from one another through the detection of virus type-specific DNA by PCR in combination with virus type-specific IgG [37]. As an example, this means that when HSV-2 is detected on genital swab in a pregnant woman, primary genital herpes can be differentiated from a recurrence up to a few weeks before delivery using HSV type-specific IgG. This differentiation is of great significance, since the risk of severe neonatal HSV infection is many times higher following primary infection than with recurrent infection. Although HSV type-specific antibody tests have been commercially available for approx. two decades they are used seldom in Germany despite the above mentioned advantages, and most laboratories only offer non type-specific HSV antibody tests [38,39]. Avidity testing can also assist in differentiating between primary and recurrent infections although to date experience with this method is limited [40]. Negative anti-HSV IgG excludes recurrent HSV infection.

**Table 1** Methods to detect HSV and HSV-specific antibody.

<table>
<thead>
<tr>
<th>Principle</th>
<th>Method</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral DNA detection</td>
<td>Polymerase chain reaction (PCR)</td>
<td>Examination material: vesicle content in virus transport medium with special swabs, liquor, tissue sample, bronchoalveolar lavage, EDTA blood, amniotic fluid, intraocular fluid</td>
</tr>
<tr>
<td>Virus isolation</td>
<td>Cultivation in cell cultures, detection/typing using monoclonal antibodies</td>
<td>Examination material: vesicle content in virus transport medium with special swabs, tissue sample, bronchoalveolar lavage</td>
</tr>
<tr>
<td>Viral antibody detection</td>
<td>Immunofluorescence test with monoclonal antibodies</td>
<td>Examination material: cell-rich vesicle content in virus transport medium with special swabs, tissue sample</td>
</tr>
<tr>
<td>Detection of type-specific and non-type-specific antibodies</td>
<td>Enzyme-linked immunosorbent assay (ELISA)</td>
<td>Determination and differentiation of IgG classes (IgG, IgM) in serum, plasma and liquor</td>
</tr>
<tr>
<td>Detection of non-type-specific antibodies</td>
<td>Indirect immunofluorescence antibody test (IFAT)</td>
<td>Detection and differentiation of IgG classes (IgG, IgM) in serum, plasma and liquor</td>
</tr>
<tr>
<td>Detection of type-specific antibodies</td>
<td>Immunoblot</td>
<td>Qualitative determination of viral type-specific IgG antibodies against viral glycoproteins (gG1, gG2) in serum</td>
</tr>
</tbody>
</table>

**Antibody detection**

The detection of virus-specific antibodies for confirming HSV infection is widely used in clinical practice. One should however be aware of the limited value of serology results. HSV serology is mainly useful for confirming seroconversion following primary infection, through demonstration of IgG. This can be of particular value in the diagnosis of HSV-2 infections in the context of antenatal care. Confirming seroconversion is also possible by demonstrating type-specific IgG antibodies, and since HSV-1 and HSV-2 are so closely related this is only possible using ELISA/immunoblot on the basis of HSV-1 gG-1 or gC-1, and HSV-2 gG-2 [2,3]. When interpreting results it is important to consider that partial cross-immunity exists between HSV-1 and HSV-2. The importance of HSV type-specific IgG is mostly that it allows rapid, reliable and economical identification of HSV-2 carriers and potential virus shedders [31,36]. Thus a patient in whom anti-HSV-2 IgG is detected can be considered a potential virus shedder and transmitter who may also suffer from anogenital HSV infection. If an initial serum sample is available from the early stage of a herpes genitalis infection, primary and recurrent infections can be differentiated from one another through the detection of virus type-specific DNA by PCR in combination with virus type-specific IgG [37]. As an example, this means that when HSV-2 is detected on genital swab in a pregnant woman, primary genital herpes can be differentiated from a recurrence up to a few weeks before delivery using HSV type-specific IgG. This differentiation is of great significance, since the risk of severe neonatal HSV infection is many times higher following primary infection than with recurrent infection. Although HSV type-specific antibody tests have been commercially available for approx. two decades they are used seldom in Germany despite the above mentioned advantages, and most laboratories only offer non type-specific HSV antibody tests [38,39]. Avidity testing can also assist in differentiating between primary and recurrent infections although to date experience with this method is limited [40]. Negative anti-HSV IgG excludes recurrent HSV infection.
sensitivity and specificity [41]. It must however be noted that the positive predictive value of anti-HSV IgM is low, and that it does not allow differentiation between primary and recurrent infection. Although IgM is usually positive following primary infection it can also be positive in the context of recurrence, independent of clinical symptoms. The rather unreliable measurement of HSV type-specific IgM antibodies should be avoided in clinical practice [41].

**Table 2** HSV laboratory findings and correlating herpes genitalis symptoms.

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>HSV serology</th>
<th>PCR</th>
<th>Interpretation/Infection status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary herpes genitalis</td>
<td>HSV-1/2 IgG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>neg.</td>
<td>neg.</td>
<td></td>
<td>acute HSV-1 infection</td>
</tr>
<tr>
<td>pos.</td>
<td>neg.</td>
<td></td>
<td>acute HSV-1 infection, latent HSV-2</td>
</tr>
<tr>
<td>neg.</td>
<td>neg.</td>
<td></td>
<td>acute HSV-2 infection</td>
</tr>
<tr>
<td>pos.</td>
<td>neg.</td>
<td></td>
<td>acute HSV-2 infection, latent HSV-1</td>
</tr>
<tr>
<td>Recurrent herpes genitalis</td>
<td>HSV-1 IgG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pos.</td>
<td>pos.</td>
<td></td>
<td>recurrent HSV-1 infection, latent HSV-2</td>
</tr>
<tr>
<td>pos.</td>
<td>neg.</td>
<td></td>
<td>recurrent HSV-2 infection, latent HSV-1</td>
</tr>
<tr>
<td>No genital herpes lesions</td>
<td>HSV-1 IgG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>neg.</td>
<td>neg.</td>
<td></td>
<td>seronegativity, susceptibility</td>
</tr>
<tr>
<td>pos.</td>
<td>neg.</td>
<td></td>
<td>previous HSV-1 infection (latent HSV-1)</td>
</tr>
<tr>
<td>pos.</td>
<td>neg.</td>
<td></td>
<td>previous HSV-2 infection (latent HSV-2)</td>
</tr>
</tbody>
</table>

**Antiviral Therapy**

**Standard treatment**

Table 3 gives an overview of antiviral drugs and dosages for the treatment of herpes genitalis according to current guidelines [31, 32, 42, 43]. Standard first-line drugs include acyclovir, valacyclovir, and famciclovir. The specific antiviral action of these acyclic nucleoside analogues [44] is based on their phosphorylation to monophosphate form by thymidine kinase (TK), the key enzyme of HSV-1 and HSV-2, with subsequent phosphorylation via diphosphosphate form by cellular enzymes. The triphosphate nucleoside analogues inhibit and fixate the viral DNA polymerase by being incorporated into the growing DNA chain as “false” enzyme.
Table 3  Antiviral treatment of herpes genitalis.

<table>
<thead>
<tr>
<th>Condition/type of treatment</th>
<th>Acyclovir</th>
<th>Valacyclovir</th>
<th>Famiciclovir</th>
<th>Foscarnet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary herpes genitalis</td>
<td>$3 \times 400$ mg p. o. daily, 7–10 days</td>
<td>$2 \times 500$ mg p. o. daily, 7–10 days</td>
<td>$3 \times 250$ mg p. o. daily, 7–10 days</td>
<td>—</td>
</tr>
<tr>
<td>Severe primary herpes genitalis</td>
<td>$5 \times 200$ mg p. o. daily, 7–10 days</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Primary herpes genitalis during pregnancy</td>
<td>$5 \times 200$ mg p. o. daily, 10 days</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Recurrent herpes genitalis (&lt; 5–6 episodes per year)$^2, 3$</td>
<td>$2 \times 800$ mg p. o. daily, 5 days</td>
<td>$2 \times 500$ mg p. o. daily, 3 days</td>
<td>$2 \times 125$ mg p. o. daily, 5 days</td>
<td>—</td>
</tr>
<tr>
<td>Recurrent herpes genitalis during pregnancy</td>
<td>$3 \times 400$ mg p. o. daily, 5 days</td>
<td>$1 \times 1000$ mg p. o. daily, 5 days</td>
<td>$2 \times 1000$ mg p. o. daily, 1 day</td>
<td>—</td>
</tr>
<tr>
<td>Recurrent herpes genitalis during pregnancy, preventive: from 36th gestational week to delivery</td>
<td>$3 \times 800$ mg p. o. daily, 2 days</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Preventive treatment before pregnancy</td>
<td>$2 \times 400$ mg p. o. daily, max. 6 months$^3$</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Prophylaxis/viral suppression (≥ 5–6 episodes per year)$^3, 4$</td>
<td>$2 \times 400$ mg p. o. daily, max. 6 months$^3$</td>
<td>$1 \times 500$ mg p. o. daily, max. 6 months$^3$</td>
<td>$2 \times 250$ mg p. o. daily, max. 6 months$^3$</td>
<td>—</td>
</tr>
<tr>
<td>Recurrent herpes genitalis with acyclovir resistance</td>
<td>$4 \times 200$ mg p. o. daily, max. 6 months$^3$</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Recurrent herpes genitalis before pregnancy, preventive: 36th gestational week to delivery</td>
<td>$3 \times 400$ mg p. o. daily, 10 days</td>
<td>$2 \times 250$ mg p. o. daily, 3 days</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Prophylaxis/viral suppression before pregnancy</td>
<td>$3 \times 250$ mg p. o. daily, 10 days; 5 days</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

$^1$ Acyclovir is not licensed for use during pregnancy (off-label use). Use should be avoided particularly before the 15th week of gestation.

$^2$ Mild presentations can also be treated topically with acyclovir or foscarnet. This is not adequate during pregnancy.

$^3$ In immunosuppressed patients (e.g. HIV) higher doses, longer treatment periods and acyclovir i.v. may be necessary.

$^4$ According to a Cochrane study [45] viral suppression/prophylaxis may already be indicated after at least 4 recurrences per year.

$^5$ Longer than 6 months in certain settings (e.g. HIV). Prerequisite for viral suppression/prophylaxis: monthly renal and liver laboratory parameters.

$^6$ Alternative: Cidofovir ($5$ mg/kg i. v. $1 \times$ weekly, later $2 \times$ weekly, off-label use); $1\%$ foscarnet cream or $1\%$ cidofovir gel topically.
choice in pregnancy [49]. In rare cases famciclovir can cause headaches, nausea and confusion.

**Alternative treatment options**

Following prolonged use of acyclovir/valacyclovir resistance, including cross-resistance to famciclovir, may develop in up to 5% of immunosuppressed or HIV positive patients [50, 51]. In such cases the pyrophosphate analogue foscarnet (Table 3) is recommended as alternative treatment [35]. Phenotypic and/or genotypic resistance testing should be performed in this situation. Foscarnet inhibits the viral DNA polymerase of numerous DNA and RNA viruses by suppression of pyrophosphate exchange. Since this substance does not need to be metabolised in order to inhibit viral replication it is also effective against TK-negative HSV strains, which are resistant to nucleoside analogues. Important side effects include renal dysfunction and toxin-induced ulcers of the urogenital mucous membranes. Since the 3 times daily i.v. application of foscarnet requires obligatory hospital admission off-label use of cidofovir i.v. once to twice weekly provides an alternative for acyclovir resistant cases (Table 3). Cidofovir is exclusively licensed for treatment of cytomegalovirus retinitis in the context of HIV, however it is also effective against HSV. Marked nephrotoxicity and a lack of clinical experience with its use in treating HSV infections are significant barriers to the use of cidofovir in clinical practice. In view of the often atypical presentation of genital herpes systemic treatment with foscarnet (or cidofovir) is generally required. Important contraindications include renal dysfunction, hypersensitivity, pregnancy and breastfeeding. When side effects or patient contraindications preclude using systemic foscarnet (or cidofovir) in a patient with acyclovir resistant herpes genitalis, topical application of 1% foscarnet cream or 1% cidofovir gel may provide an effective alternative [52].

The helicase blockers, a new class of drug that is currently still in clinical development and testing, may improve the antiviral treatment of herpes genitalis significantly in future. Thus far effective inhibition of HSV replication has been demonstrated in cell cultures, animal models and initial clinical studies without evidence of major side effects. It is thought that helicase blockers bind to the helicase-primase complex, a protein component essential for virus replication, effectively inhibiting DNA synthesis and thus viral replication. Indeed, better results have been achieved in vitro and in vivo than for acyclovir and valacyclovir. For oral pritelivir (BAY 57-1293, AIC316) a significant reduction of clinical symptoms and HSV-2 shedding was shown in herpes genitalis patients [53]. Helicase blockers have also been shown to be effective against acyclovir resistant HSV strains [54].

**Resistance testing**

Clinical treatment failure is defined as lack of response to antiviral treatment (usually acyclovir/valacyclovir) within 10 days. In such cases infection with a resistant strain of virus should be suspected [55] and phenotypic and/or genotypic resistance testing performed. These specialised investigations are performed routinely at the HSV and VZV consulting laboratory. In the presence of acyclovir/valacyclovir resistance, which is almost always associated with cross-resistance to famciclovir, alternative treatment with foscarnet is indicated [56]. Phenotypic resistance tests in particular are time consuming, requiring at least 7–10 days, so that when severe resistance is present clinically appropriate changes to treatment should not be delayed until results become available.

In the published literature plaque reduction/cytopathic effect inhibiting tests, dye uptake assays and DNA hybridisation assays have been described, plaque reduction being the most commonly used method [56]. The sensitivity of HSV to virostatic agents can be measured on the basis of inhibition of morphologically induced, virus-specific cell changes; so-called cytopathic effects. By testing the antiviral agent in a geometric dilution series in descending order the agent’s mean inhibitory concentration (ICSO), which results in 50% inhibition of viral replication, is calculated. Largely due to the biological disturbance variable “cell culture” there is currently no internationally standardised cut-off defining resistance. It is therefore necessary to run a control using a TK-positive reference strain along with each test. Most commonly and reliably resistance to nucleoside analogues and cidofovir is assumed when the IC50 of the tested HSV strain is 3 to 5-times higher than that of the sensitive control strain [57, 58]. For foscarnet a set cut-off of 330 µM has proven useful [59]. The main advantage of phenotyping is that the interpretation of results is unequivocal, which is why this method continues to be regarded as the gold standard for HSV resistance testing. Disadvantages include the fact that it is time consuming, the high cost of materials needed for isolation and testing of HSV strains in cell cultures, and the lack of standardisation. Phenotypic resistance testing is practically only possible when vesicle or respiratory tract swabs are available from which HSV can be easily isolated. In the majority of cases attempts to isolate the virus from liquor, blood or eye samples are unsuccessful.

Genotypic resistance testing usually involves amplification and sequencing of the TK and DNA polymerase genes [56]. The data are then compared to a sensitive reference strain from the gene bank (e.g. HSV-1 strain 17 accession no. X14112, HSV-2 strain HG52 accession no. Z86099). Findings suggestive of resistance include frameshift mutations, extra stop codons and non-synonymous nucleotide substitutions in conserved and functionally important gene regions. Interpretation of amino acid substitutions outside of active or conserved gene regions requires access to a database in which all resistance mutations described in the literature are pooled [56]. HSV-1 and HSV-2 resistance to acyclovir/valacyclovir/famciclovir is almost always associated with non-synonymous mutations of the TK gene and only rarely the DNA polymerase gene, while resistance to foscarnet/cidofovir is exclusively associated with mutations to the DNA polymerase gene. Matching of resistance pheno- and genotypes of HSV isolates is the most reliable and practical method available for confirming the resistance associations of new, as yet unknown amino acid substitutions. The essential advantage of genotyping is that direct testing of patient samples is performed, making virus isolation in cell culture unnecessary. Depending on virus load results may be available within two days, which is of immense importance for clinical decision-making.

**Prophylaxis**

**Vaccination**

The question of possible immunisation is often raised not only by doctors but also by many patients affected by herpes genitalis. To date, however, there is no licensed vaccine against herpes genitalis, though research has been ongoing for a number of decades. “Therapeutic” vaccines are differentiated from “prophylactic” vaccines depending on their modes of action. Whereas therapeutic vaccines aim to prevent recurrent HSV infections and symp-
matic viral shedding in people with latent HSV infection, prophylactic vaccines are intended to prevent primary infection and subsequent virus latency. Here HSV-2 has been the main focus of research. A large number of vaccines have been tested in vaginal animal models (mouse and guinea pig) [60], though currently vaccines based on recombinant viral proteins appear to be the most promising [61]. Randomised placebo-controlled trials of adjuvant HSV-2 protein subunit vaccines [62,63] and live attenuated HSV-2 deletion mutants [64,65] in humans have not produced results convincing enough to justify the licensing of a vaccine. Although these vaccines are not associated with a risk of vaccine virus infection and latency, there have been significant difficulties in meaningfully reducing the number of recurrences and preventing primary genital infection with both HSV-1 and HSV-2. There is hope in the knowledge that protection from primary infection is chiefly mediated by virus-specific antibodies, while cell-mediated immunity is of greatest importance in the prevention of recurrence [60,66]. Thus vaccine-induced cellular immunity must be stronger than that following natural HSV infection.

Other methods

Sound, comprehensive partnership counselling is an essential component of the medical management of herpes genitalis patients. For this, HSV type-specific serology is an important tool as it allows identification of the HSV-2 carrier. If no HSV-2-specific antibodies can be detected in the partner of an HSV-2 seropositive person the couple should be advised to use condoms [67]. If herpes genitalis symptoms are present sexual intercourse should be discouraged [68]. Since these measures are particularly important for the prevention of viral transmission during pregnancy both partners should be informed about their HSV serostatus and the possible consequences of viral transmission, both with symptomatic herpes genitalis and asymptomatic viral shedding. Psychotherapy can help reduce the number of herpes genitalis recurrences in women with high levels of emotional stress. In future microbiocides in the form of gels, creams or lotions may be an option for the prevention of herpes virus transmission via sexual intercourse. The best studied substance for this method of herpes genitalis prevention is tenofovir, a nucleoside analogue reverse transcriptase inhibitor licensed for treatment of HIV infection. Studies have shown that vaginal application of tenofovir gel 12 hours before sexual intercourse prevents HSV-2 infection in HSV-2-negative women [69] but does not prevent asymptomatic viral shedding or genital symptoms in women with known herpes genitalis [70]. VivaGel® is another promising microbiocide that inhibits HSV replication following vaginal application. This product contains the nanotechnologically manufactured dendrimer SPL7013 as its active substance [71]. However, at best these microbiocides will constitute supplementary options for future herpes genitalis prevention.

Practical Conclusions

The medical management of patients with herpes genitalis is often unsatisfactory. It can be significantly improved through competent patient counselling and correct implementation of existing methods of diagnosis, treatment and prevention. Nevertheless currently available antiviral treatment and prophylaxis still has shortcomings, especially in the management of frequent recurrences. A new drug class – the helicase blockers – and the development of effective vaccines are expected to improve the situation significantly in future.

Conflict of Interest

None.

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