Herpes Genitalis: Diagnosis, Treatment and Prevention
Diagnostik des Herpes genitalis, einschließlich antiviraler Therapie und prophylaktischer Möglichkeiten

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

Sauerbrei A. Herpes Genitalis: Diagnosis, ... Geburtsh Frauenheilk 2016; 76: 1310–1317
reason for this it has been suggested that men have asymptomat-
ic 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 infec-
tion is associated with an increased risk of HIV infection [10].

Virus Transmission and Infection

Primary herpes genitalis

Primary genital infections with HSV-1 and HSV-2 are usually
asymptomatic [11]. The classical clinical features consist of mac-
ular or papular skin and mucous membrane lesions occurring ap-
prox. 4–7 days after sexual contact; these progress to vesicles,
pustules and ulcers and can last for up to 3 weeks. [12]. Typical
symptoms also include pain, especially painful inflammatory
swelling of the vulva in women, burning pain and dysuria.
Lymphadenopathy, fever and cervicitis (in women)/proctitis (in
men) are relatively common associated symptoms. Genital her-
pes may manifest atypically, particularly in the female genital
tract, making the clinical diagnosis far more difficult. Signs of
herpes lesions of the cervix are relatively common in the absence
of symptoms, where urethral manifestations are often associated
with severe micturition problems.

Recurrent herpes genitalis

Following the primary eruption the virus establishes lifelong la-
tency in sensory neural ganglions [13]; in the case of primary
genital infection the sacral ganglions are mainly involved. From
here the virus can reactivate, causing recurrent infection. Viral
reactivation is common in the presence of immunogenetic pre-
disposition, though reactivations decrease with increasing age.
Numerous physiological and environmental factors such as fever,
UV light, menstruation, stress or trauma can function as triggers
[14, 15]. Endogenous viral reactivations may manifest as recur-
rent herpes genitalis. Recurrences occur in almost every person
suffering symptomatic primary herpes genitalis due to HSV-2, in
a third of patients frequently (at least 6 times a year) [16]. Recur-
rent genital HSV-1 infections occur over five times less com-
monly [17]. Recurrences almost always initially present with
prodromal symptoms such as neuralgic symptoms, dysesthesia
or lumbosacral dermatome pain 1–2 days before skin and mu-
cosal lesions erupt [18]. Compared to primary infection, symp-
toms of recurrence are much less severe and the clinical course
shorter [19]. In the experience of the reference laboratory for
HSV and VSV of the Institute for Virology and Antiviral Therapy
of the University Hospital of Jena, in its advisory capacity, fre-
quent herpes genitalis recurrences particularly affect young
women with a high burden of stress in the family and workplace.
It must also be taken into account that recurrences themselves
can cause high levels of emotional stress [20]. Affected patients
and their sexual partners therefore more commonly suffer signif-
icant psychosocial problems.

Asymptomatic genital viral shedding

In the majority of cases endogenous viral reactivation is charac-
terised 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 con-
trast, HSV-1 shedding is uncommon. These data allow the as-
sumption, 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 asymptomatically can transmit the virus
to their sexual partners. This almost always occurs via direct con-
tact during sexual intercourse. In recent years an increased inci-
dence 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 environ-
mental 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 body-
ly hygiene) is maintained, modes of transmission other than sex-
ual 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 in-
trauterine 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 de-
scribed include abortion, stillbirth or other congenital manifesta-
tions 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 infec-
tion. 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 inci-
dence 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 mani-
fests as localised infection of the skin, eyes and mucous mem-
branes, 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 iso-
lation, in which case cooling is recommended.

Virus detection

The laboratory diagnosis of acute genital HSV infection or asym-
tomatic 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-

Sauerbrei A. Herpes Genitalis: Diagnosis, ... Geburtsh Frauenheilk 2016; 76: 1310–1317
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 herpetic 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 Ig 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 Ig 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, gC2) 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 herpetic 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 2** provides a summary of virology and serology findings for the laboratory diagnosis of HSV infections with or without genital lesions and for asymptomatic viral shedding.
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]. 

Fig. 1 provides a summary of the recommended viral diagnostic algorithm for herpes genitalis.

### 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 neg. neg. neg. pos. neg.</td>
<td>HSV-1 IgG</td>
<td>acutue HSV-1 infection</td>
</tr>
<tr>
<td></td>
<td>HSV-1 IgG pos. neg. pos. neg.</td>
<td>HSV-1</td>
<td>acute HSV-1 infection, latent HSV-2</td>
</tr>
<tr>
<td></td>
<td>HSV-2 IgG neg. neg. neg. pos.</td>
<td>HSV-2</td>
<td>acute HSV-2 infection</td>
</tr>
<tr>
<td></td>
<td>HSV-1 IgG pos. pos. neg. neg.</td>
<td>HSV-1</td>
<td>acute HSV-2 infection, latent HSV-1</td>
</tr>
<tr>
<td>Recurrent herpes genitalis</td>
<td>HSV-1 IgG pos.</td>
<td>pos. neg.</td>
<td>recurrent HSV-1 infection (recurrence)</td>
</tr>
<tr>
<td></td>
<td>HSV-2 IgG neg. pos.</td>
<td>pos.</td>
<td>recurrent HSV-2 infection (recurrence)</td>
</tr>
<tr>
<td></td>
<td>HSV-2 IgG pos.</td>
<td>pos.</td>
<td>recurrent HSV-2 infection, latent HSV-1</td>
</tr>
<tr>
<td>No genital herpes lesions</td>
<td>HSV-1 IgG pos.</td>
<td>pos. neg.</td>
<td>previous HSV-1 infection (latent HSV-1)</td>
</tr>
<tr>
<td></td>
<td>HSV-2 IgG pos.</td>
<td>neg. neg. neg. neg.</td>
<td>previous HSV-2 infection (latent HSV-2)</td>
</tr>
<tr>
<td></td>
<td>HSV-1 IgG neg. neg. neg. neg.</td>
<td>HSV-1</td>
<td>previous HSV-1 and HSV-2 infection (latent HSV-1)</td>
</tr>
<tr>
<td></td>
<td>HSV-2 IgG neg. neg. pos. pos.</td>
<td>HSV-2</td>
<td>previous HSV-1 and HSV-2 infection (latent HSV-1)</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 diphosphate 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.
substrates. In the case of acyclovir/valacyclovir this leads to chain termination, since hydroxyl groups in the 3’ position, which are essential for further linkage, are missing. Famiciclovir may be incorporated into the growing DNA chain.

Acyclovir is the first choice therapeutic agent for HSV infections, including herpes genitals. However bioavailability is only 15–30% with oral administration. Infections of the skin and mucous membranes including herpes genitals are treated orally in immunocompetent people. Severe HSV infections, particularly in immunodeficient patients, should be treated with intravenous (i.v.) acyclovir. Acyclovir dosage for the treatment of herpes genitals is dependant on infection status, immune competence and whether or not the patient is pregnant. If recurrences occur at a rate of over four [45] to six episodes annually [31, 32, 42, 43] long-term treatment to suppress the virus (prophylaxis) should be considered. The benefits of prophylaxis have been proven particularly during pregnancy [46]. Topical acyclovir is only recommended for herpes labialis, herpes keratoconjunctivitis and mildly symptomatic herpes genitals. Officially acyclovir is not licensed for use in pregnancy, though administration should be avoided particularly before the 15th week of gestation [22]. Results from a pregnancy register published by an acyclovir producer and the Centers for Disease Control and Prevention (USA) [47] as well as results of a retrospective cohort study in Denmark [48] have shown, however, that oral and topical acyclovir do not appear to increase the rate of congenital anomalies. Since these data are not sufficient for general authorisation, particularly in early pregnancy, pregnant patients must be informed about the limited evidence on use in pregnancy (off-label use). Occasional central nervous system side effects have been described following i.v. acyclovir administration and oral acyclovir may produce gastrointestinal side effects. Nephrotoxic substances should not be administrated concurrently and both renal and liver laboratory parameters should be monitored.

Valacyclovir is a prodrug (an L-valyl ester) of acyclovir suitable for oral administration. After ingestion it is converted to acyclovir by the hepatic enzyme valacyclovir hydrolase. Oral valacyclovir has a bioavailability of 54%, achieving active ingredient concentrations three to four times higher than oral acyclovir. This allows increased dose intervals and is associated with better compliance. Valacyclovir is also a standard treatment for herpes genitals in immunocompetent patients and studies have shown its efficacy for viral suppression and prevention of recurrent herpes genitals [46]. Valacyclovir is not licensed for antiviral treatment in children and adolescents since its efficacy and safety profiles have not yet been adequately studied in this population. This applies to pregnancy too as there is also little data on its safety in this context [48]. Possible side effects are similar to those of acyclovir.

Famiciclovir is the inactive diacetyl ester prodrug of the only topically effective acyclic nucleotide analogue penciclovir, which arises after cleavage of two ester groups in the small bowel and liver. The bioavailability of famciclovir is 54%, achieving active ingredient concentrations three to four times higher than oral acyclovir. Famiciclovir is also regarded as one of the standard therapeutic agents for herpes genitals, along with acyclovir and valacyclovir, and is also not licensed for use in children and adolescents, immunosuppressed patients under the age of 25 years or in pregnancy. It should therefore not be used as the treatment of

### Table 3 Antiviral treatment of herpes genitals.

<table>
<thead>
<tr>
<th>Condition/type of treatment</th>
<th>Acyclovir</th>
<th>Valacyclovir</th>
<th>Famciclovir</th>
<th>Foscarnet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary herpes genitals</td>
<td>3 × 400 mg p. o. daily, 7–10 days</td>
<td>2 × 500 mg p. o. daily, 7–10 days</td>
<td>3 × 250 mg p. o. daily, 7–10 days</td>
<td></td>
</tr>
<tr>
<td>Severe primary herpes genitals</td>
<td>5 × 200 mg p. o. daily, 7–10 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary herpes genitals during pregnancy</td>
<td>5 × 200 mg p. o. daily, 10 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent herpes genitals (&lt; 5–6 episodes per year)</td>
<td>2 × 800 mg p. o. daily, 5 days</td>
<td>2 × 500 mg p. o. daily, 3 days</td>
<td>2 × 125 mg p. o. daily, 5 days</td>
<td></td>
</tr>
<tr>
<td>Recurrent herpes genitals during pregnancy</td>
<td>3 × 400 mg p. o. daily, 5 days</td>
<td>1 × 1 000 mg p. o. daily, 5 days</td>
<td>2 × 1 000 mg p. o. daily, 1 day</td>
<td></td>
</tr>
<tr>
<td>Recurrent herpes genitals during pregnancy</td>
<td>3 × 800 mg p. o. daily, 2 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preventive treatment before pregnancy</td>
<td>2 × 400 mg p. o. daily, max. 6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylaxis/viral suppression (≥ 5–6 episodes per year)</td>
<td>2 × 400 mg p. o. daily, max. 6 months</td>
<td>1 × 500 mg p. o. daily, max. 6 months</td>
<td>2 × 250 mg p. o. daily, max. 6 months</td>
<td></td>
</tr>
<tr>
<td>Recurrent herpes genitals with acyclovir resistance</td>
<td>4 × 200 mg p. o. daily, max. 6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 × 40</td>
<td></td>
</tr>
</tbody>
</table>
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 achieved in vitro and in vivo than for acyclovir and valacyclovir. And thus viral replication. Indeed, better results have 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 (IC50), 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 data bank 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-
omatic 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 microbicides 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 microbicide that inhibits HSV replication following vaginal application. This product contains the nanotechnologically manufactured dendrimer SPL7013 as its active substance [71]. However, at best these microbicides 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.

References

3 Scheppe T, Saschenbrecker S, Steinhagen K et al. The glycoproteins C and G are equivalent target antigens for the determination of herpes simplex virus type 1-specific antibodies. J Virol Methods 2010; 166: 42–47
8 Roberts CM, Pfister JR, Spear SJ. Increasing proportion of herpes simplex virus type 1 as a cause of genital herpes infection in college students. Sex Transm Dis 2003; 30: 797–800
10 Freeman EE, Weiss HA, Glynn JR et al. Herpes simplex virus 2 infection increases HIV acquisition in men and women: systematic review and meta-analysis of longitudinal studies. AIDS 2006; 20: 73–83
17 Engelberg R, Carrell D, Krantz E et al. Natural history of genital herpes simplex virus type 1 infection. Sex Transm Dis 2003; 30: 174–177
30 LeGoff J, Pérez H, Bénec L. Diagnosis of genital herpes simplex virus infection in the clinical laboratory. Virol J 2014; 11: 83
48 Pasternak B, Hvidt A. Use of acyclovir, valacyclovir, and famciclovir in the first trimester of pregnancy and the risk of birth defects. JAMA 2010; 304: 859–866
71 Price CF, Jyssen D, Sonza S et al. SPL7013 Gel (VivaGel®) retains potent HIV-1 and HSV-2 inhibitory activity following vaginal administration in humans. PLoS One 2011; 6: e24095