Genital Herpes

Editor and Contributor:
Matthew F. Davies, MD, FACOG
Associate Professor, Department of Obstetrics and Gynecology
Pennsylvania State University College of Medicine; Chief, Division of Women’s Health; Director of Labor and Delivery; The Penn State Milton S. Hershey Medical Center, Hershey, PA

Contributor:
Colin MacNeill, MD
Assistant Professor, Pennsylvania State University College of Medicine; Staff Physician, The Penn State Milton S. Hershey Medical Center, Hershey, PA

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INTRODUCTION

Genital herpes is a sexually transmitted infection caused by herpes simplex virus (HSV). Although HSV-2 causes the majority of cases, HSV-1 can also cause genital herpes. Genital herpes is now the most prevalent of the sexually transmitted diseases (STDs), affecting 45 million persons in the United States. In addition, the incidence of genital herpes infections in the United States is currently estimated to be 1 million new cases per year and is rapidly increasing. This inordinately high incidence can be explained by failure to identify patients with genital HSV infection. In fact, it is estimated that less than 20% of HSV-2 seropositive patients have been diagnosed. As a result, the risk of disease transmission to the sexual partners of infected patients is not being appropriately managed.

Managing patients with genital herpes involves preventing viral transmission to seronegative sexual partners as well as neonates, but this falls short for 2 reasons, both directly related to disease recognition. It is now known that there exists a large number of patients in whom asymptomatic viral shedding occurs. Before viral shedding could be detected by sensitive polymerase chain reaction (PCR) methods, it was believed that there was little or no shedding in asymptomatic patients. Secondly, atypical lesions that are not readily identified as herpes lesions are highly prevalent. In a study performed at an STD clinic, only 60% of patients with positive HSV-2 cultures had typical external lesions. Underrecognition of these 2 critical factors, for which practitioners bear at least some blame, contributes greatly to the rapid spread of genital HSV infection in that failure to recognize disease precludes preventive interventions.

This review examines characteristics of HSV biology that contribute to the high incidence of genital herpes and highlights how the syndrome is changing epidemiologically. Approach to clinical diagnosis and current recommendations for managing patients with genital HSV infection are discussed, and the status of developing treatment strategies is reported.

EPIDEMIOLOGY

RECENT CHANGES IN HSV EPIDEMIOLOGY

The most striking change involving genital herpes in the past 20 years is the rapid increase in HSV seroprevalence (ie, proportion of the population seropositive for antibodies to HSV). Seroprevalence is the best indicator of disease burden. According to the National Health and Nutrition Examination Surveys (NHANES) II and III, HSV seroprevalence in the United States increased from 16% in 1980 to 22% in 1994. Many other developed countries also have reported increases in seroprevalence. For example, Lowhagen et al found that the age-adjusted HSV-2 seroprevalence among pregnant women in Sweden in 1973 was 13% and had increased to 24% in 1989. It is important to note that very few studies compare identical populations and use similar methodologies to allow direct comparisons. However, the NHANES studies do use similar methods and populations, and while other Swedish studies find larger or smaller increases in seroprevalence, they support the NHANES finding that the seroprevalence of HSV is increasing.

TRENDS IN HSV SEROPREVALENCE

Analysis of US seroprevalence data, which calculates the strength of the association between HSV positivity and each factor within a specific population using multiple logistic regression, has elucidated several trends associated with HSV-1 and HSV-2 acquisition. For example, seroprevalence rises rapidly from 5% to 17% in patients between ages 20 and 29 years and is up to 28% in patients between ages 30 and 39 years, which is not unexpected given that during these years the number of sexual partners increases. A study of first- and second-year US college students also elucidated significant predictors of risk for HSV seropositivity for this population (Table 1). It has also been observed that the seroprevalence of HSV-2 is higher in the US general population than in the general European population but is lower than that of most developing
countries. Although these associations have not yet been clearly defined in the United States, it has been noted that seroprevalence rates vary widely among countries within a specific region and can even vary widely within an individual country. In a large random sample from Norway, seroprevalence was 26% overall but varied geographically from 18% in the south to 39% in the north. Regardless of geographic location, women consistently have been found to have a higher HSV seroprevalence than men.

**SEROCONVERSION**

The largest contributing factor to an increasing seroprevalence is the correspondingly high incidence of HSV infection, or in serologic terms, the rate of seroconversions. Incidence is the number of new cases of infection, in this case HSV infections, occurring during a given span of time in a population at risk. However, determining the number of seroconversions, and therefore seroprevalence, is difficult for several reasons. Genital herpes is not a reportable disease in the United States, so population incidence data do not exist. Also, a large percentage of seroconverted patients are asymptomatic. Studies have identified patients with new HSV-2 infections by demonstrating seroconversion in cohorts of at-risk subjects, but these studies are small, expensive to conduct and may not represent the general at-risk population.

Another serious impediment to accurately determining the rate of seroconversions is related to the biology of the virus: the seropositive sexual partners of at-risk seronegative persons are periodically shedding virus particles in the absence of symptoms. In a study by Mertz and colleagues, transmission of genital herpes was linked to sexual contact during periods of asymptomatic shedding in 70% of patients. These asymptomatic seropositive patients, unaware that they are actively infectious, are in many cases not using prophylactic measures to decrease transmission—measures that are imperfect at best. In fact, many seropositive patients are unaware of their seropositive status altogether. In a study of 2393 seronegative patients, the rate of newly acquired HSV-2 infection was 5.1 cases per 100 person-years. In this group of 155 patients, 63% were also HSV-1 positive. Only 37% of the 155 new HSV-2 positive infections were symptomatic, meaning that most patients were unaware of their seropositive status because they did not experience bothersome symptoms and, therefore, did not seek medical attention. The presence of HSV-1 had no effect on the HSV-2 seroconversion rate, but importantly, those with a prior HSV-1 infection were 3 times more likely to be asymptomatic.

**Table 1. Significant Predictors of HSV Seropositivity in First- and Fourth-Year US College Students**

<table>
<thead>
<tr>
<th>Predictors of Seropositivity</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV-1</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2.3</td>
</tr>
<tr>
<td>6 Years of sexual experience</td>
<td>3.0</td>
</tr>
<tr>
<td>Partner with oral sores</td>
<td>2.4</td>
</tr>
<tr>
<td>Prior STI</td>
<td>2.0</td>
</tr>
<tr>
<td>HSV-2</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.6</td>
</tr>
<tr>
<td>3–5 Years sexual experience</td>
<td>18.4</td>
</tr>
<tr>
<td>African-American race</td>
<td>4.6</td>
</tr>
<tr>
<td>Prior STI</td>
<td>3.4</td>
</tr>
</tbody>
</table>


HSV = herpes simplex virus; STI = sexually transmitted infection.

Despite the difficulties in detecting seroconversions, there have been some improvements in identifying newly infected patients. The availability of HSV type-specific antibodies has facilitated the identification of those at risk for asymptomatic first episode disease as well as cases of HSV-1 genital herpes in certain populations. Also, the significantly increased sensitivity of PCR-based methods over traditional culture methods for detecting HSV in genital lesions has contributed greatly. In a study of genital isolates from a US university health service, the proportion of newly diagnosed genital infections due to HSV-1 increased from 31% in 1993 to 78% in 2001. It is not clear at present whether this increased incidence of genital HSV-1 infection stems from a change in sexual practices, as is suspected by a positive association of HSV-1 with receptive oral sex and a negative association with vaginal sex. It does seem clear, based on the work of Langenberg and colleagues, that increased HSV-1 seroprevalence will contribute substantially to asymptomatic HSV-2 acquisition.

**PATHOGENESIS AND COURSE OF INFECTION**

**ANTIGENICITY**

In order to understand why genital herpes is so infrequently recognized, it is necessary to understand the antigenic relationships among HSV proteins and host response to them. HSV is a linear double-strand
DNA virus that encodes 84 proteins. HSV-1 and HSV-2 share an overall 50% sequence homology that is spread over the entire genome, and most of the proteins of 1 type of HSV are antigenically related to the other. This relationship allows for the partial degree of protection that exposure to 1 type of HSV affords to the other type. There are, however, several type-specific regions that may provide an opportunity to distinguish the 2 types diagnostically and, potentially, therapeutically.

**TRANSMISSION**

Herpesvirus contact with traumatized skin or mucosa allows entry of the virus into cells of the epidermis and dermis. Upon replication and release, viral particles infect sensory and autonomic nerve endings. Infection of neuronal cells does not always result in cell death. In surviving neurons, the virus transcribes only a limited set of proteins, maintained in a repressed or latent state in which the host neuron is fully functional. In certain conditions, such as exposure to ultraviolet light, ganglia trauma, and immunosuppression in experimental animals, viral transcription becomes fully active, and viral particles are released in a process called reactivation. Viral particles released from neurons (also called viral shedding) subsequently enter epithelia and precipitate recurrence, which may or may not be marked by symptoms of genital herpes. Latency also contributes to asymptomatic shedding and results in the high and increasing HSV incidence.

**COMPLICATIONS OF HSV INFECTION**

The most devastating sequela of herpes genitalis is transmission to an infant during childbirth and subsequent neonatal herpes infection (see “Genital Herpes and Pregnancy”). Less devastating but similarly important to public health are the sequelae of recurrent infection and the newly recognized increased risk of HIV transmission in HSV seropositive patients.16

**Recurrence**

HSV infections can be classified as primary, nonprimary first episode, and recurrent. As the name suggests, a primary episode refers to the initial outbreak of lesions following seroconversion, whereas a nonprimary first episode refers to a first outbreak of HSV lesions in a person who already has acquired HSV antibodies from a previous asymptomatic infection with herpesvirus. The terms are primarily used to note a clinical distinction. Recurrence, however, is a common complication of genital herpes and, therefore, requires further discussion.

Recurrent herpes genitalis is a well-known phenomenon first described by Hippocrates. Two features of recurrent HSV infection have been discovered in the past 5 to 6 years, largely due to the availability of type-specific antibodies and to the increased sensitivity of PCR-based detection methods. One finding is that most recurrent disease is caused by HSV-2.17 Although the initial presentations of HSV-1 and HSV-2 genital herpes are quite similar, first-year recurrences average at 4 episodes in HSV-2 cases and 1 episode in HSV-1 cases. In following years, recurrences are generally limited to those caused by HSV-2, and HSV-1 recurrences are rare. Furthermore, it is common that patients infected with HSV-1 acquire new HSV-2 infections, whereas HSV-2 seropositive patients rarely contract HSV-1 herpes genitalis. As was discussed in greater detail earlier (see “Epidemiology”), a sequela to prior infection with HSV-1 in any location is that newly acquired HSV-2 is much more likely to cause asymptomatic disease and thus more likely to contribute to the spread of disease.12 Together, these features indicate that viral type has prognostic significance for frequency of recurrence and disease transmission and should be determined for every patient.18

The second discovery involves frequency of recurrences. It was axiomatic that HSV recurrences continued for the life of the infected patient. Recent studies, however, have documented that recurrence frequency in many cases decreases with time after primary infection. Benedetti and colleagues19 conducted a prospective observational study of the frequency of genital HSV reactivation in a cohort of 664 patients followed for at least 14 months. They found that median recurrence rates in the first year following newly acquired infection were once each year for HSV-1 and 5 times each year for HSV-2. Patients with HSV-2 who were followed for more than 4 years had an average of 2 less recurrences between year 1 and year 5, representing a 50% decrease. The population of patients under study could be divided into 2 groups. Most patients experienced a decrease of 1 recurrence per year between years 1 and 5; however, a smaller group (almost 25%) of patients, had at least 1 more recurrence in year 5 than in year 1. Interestingly, the decreases in the number of recurrent episodes over time in patients who had never received suppressive therapy were similar to decreases during untreated periods in patients who had been given suppressive therapy. Together, these findings suggest that patients who are receiving chronic suppressive antiviral therapy may benefit from stopping therapy and reasessing the need for it after 3 to 5 years of follow-up.

**Synergism of HSV and HIV**

During the late 1980s, it was first postulated that
chronic ulcerative diseases, such as herpes genitalis, may confer increased risk for HIV infection. Conversely, increased HSV activity in HIV-infected patients was evident early on, as perianal herpes ulcers were the first recognized opportunistic infection marking the progression of HIV infection to AIDS. Since these early observations, several facets of the relationship between HSV and HIV have come to light. One is that the natural history of HSV-2 infection is altered in persons coinfected with HIV. Such patients experience more frequent clinical and subclinical reactivation of HSV than patients infected only with HSV-2. Moreover, severity of genital herpes may be greater and disseminated HSV disease is seen more frequently.

There are accumulating data to suggest that a significant biological interaction between these 2 viruses results in more efficient sexual transmission of HIV and an increased rate of HIV replication during both clinical and subclinical HSV reactivation. For example, HSV-2 and HIV coinfection was associated with a 0.5 log copies/mL higher HIV viral load compared with HIV infection alone (P = 0.014). These data and similar findings indicate that chronic HSV-2 infection has a negative effect on the clinical course of persons with HIV and has led to trials aimed at improving HIV clinical course by decreasing HSV viral shedding and recurrence. Schacker and colleagues measured HIV viral load in patients prior to, during, and after HSV suppression with high-dose acyclovir to determine whether HSV suppression was associated with a decrease in HIV replication. Most (25 of 27 HSV/HIV coinfected persons) patients experience reactivation of HSV infection. Plasma HIV RNA load was strongly correlated with total HSV shedding rate, and the plasma HIV RNA level at a given CD4+ cell count decreased by 48% with acyclovir treatment, thus suggesting that frequent mucosal HSV reactivation influences HIV replication in vivo and that daily HSV suppression may be important in the management of HSV/HIV coinfected persons.

The question arises whether the reduction in HIV load was the result of decreased HSV activity or a direct effect of acyclovir on HIV activity. Early evidence in patients taking highly active antiretroviral therapy (HAART) suggests the latter. HAART has little direct effect on HSV but a substantial effect on HIV. Lee and colleagues performed a retrospective review of 30 patients who had taken a regimen of HAART with acyclovir and had subsequently discontinued acyclovir. Ten of these patients had documented outbreaks of genital herpes while receiving HAART; however, there was no significant rise in HIV viral load. This preliminary finding suggests that acyclovir may not confer an immunologic advantage beyond control of genital herpes outbreaks, although it must be kept in mind that this is no small advantage in terms of disease control and patient quality of life.

## Diagnosis and Treatment of Genital Herpes in the Nongravid Patient

### Case 1

**Initial Presentation and History**

A 24-year-old woman presents with new onset of vulvar burning and irritation, which began 2 to 3 days prior to presentation and has subsequently worsened. Upon questioning, she denies new contact with soaps or astringents; recent antibiotic use; and fever, chills, or other symptoms. She reports that there is no hematuria, but there is a burning sensation when urine comes in contact with the vulva. The patient has never had a yeast infection, and she is in a sexually monogamous relationship. She has not tried any over-the-counter medications for treating her symptoms.

**Physical Examination**

On physical examination, the patient has some obvious discomfort. She is afebrile. Abdominal examination is benign, and lymph node examination reveals a tender left inguinal adenopathy, which she had not previously noticed. On pelvic examination, there is diffuse erythema of the vulva and excoriation over the surface. No discrete lesions are appreciated. The vagina likewise is erythematous and has a profuse white discharge consistent with yeast infection.

**Initial Treatment and Follow-up**

The patient is treated with a 7-day course of over-the-counter imidazole for monilial vulvovaginitis. Despite some early relief, the patient presents again, stating that there is still intense burning of the vulva that has become so irritated that blisters have developed. The patient is concerned she has developed an infection where the skin was open. On repeat examination, the vulva is still erythematous but less so than before. Erythema is now localized to discrete areas surrounding multiple open ulcers with flat, encrusted bases. The lesions are tender to palpation. Several lesions are cultured for herpesvirus. Due to suspicion for HSV, the patient is started on oral antiviral therapy.

- **How is genital herpes diagnosed?**

Genital herpes is suspected when patients present with numbness and/or tingling pain in the genital

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Table 2. Clinical Characteristics of Infectious Causes of Genital Ulcer Disease (GUD)

<table>
<thead>
<tr>
<th>GUD Syndrome</th>
<th>Etiologic Agent</th>
<th>Classic Ulcer Characteristics</th>
<th>Incubation (days)</th>
<th>Pain</th>
<th>Adenopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV</td>
<td>HSV-2 in most cases, HSV-1 is less common</td>
<td>Multiple, small, grouped vesicles; erythematous base; vesicles can open forming shallow ulcers/erosions that may coalesce</td>
<td>2–7</td>
<td>Usually</td>
<td>Reactive nodes common</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Treponema pallidum</td>
<td>Indurated, smooth, firm borders; clean base; heals spontaneously; usually singular, although multiple chancres can occur in HIV-infected patients</td>
<td>7–90</td>
<td>Usually not</td>
<td>Firm, rubbery nodes; not tender; regional; discrete</td>
</tr>
<tr>
<td>Chancroid</td>
<td>Haemophilus ducreyi</td>
<td>Sharply circumscribed or irregular, ragged, undermined edges; not indurated; base may have gray or yellow exudates; multiple ulcers</td>
<td>3–10</td>
<td>Marked</td>
<td>50% with inguinal adenopathy; usually unilateral; often painful; may suppurate/rupture</td>
</tr>
<tr>
<td>LVG</td>
<td>Chlamydia trachomatis L1–L3</td>
<td>Usually not observed; small and shallow; rapid spontaneous healing</td>
<td>5–21</td>
<td>Usually not</td>
<td>More common in males; matted clusters; unilateral or often bilateral; large painful fluctuant “bubo”; painful groove sign; sinus tracts common</td>
</tr>
<tr>
<td>Granuloma inguinale</td>
<td>Calymmatobacterium granulomatis</td>
<td>Extensive, progressive; granulation-like tissue; rolled edges</td>
<td>7–90</td>
<td>Usually not</td>
<td>Pseudobuboes</td>
</tr>
</tbody>
</table>

Courtesy of Donna Felsenstein, MD, and Sonia Nagy, MD.

HSV = herpes simplex virus; LVG = lymphogranuloma venereum.

area. Suspicions are strengthened when visual examination reveals typical fluid-filled vesicles (blisters), individually or in clusters (Figure 1). In many cases, the blisters open in 7 to 10 days and subsequently form ulcers with flat, encrusted bases (Figure 2). The change seen in the case patient represents a typical rate of progression in HSV lesions. Lesions often are atypical and can appear as a focal papular or flat rash that can be indistinguishable from several other conditions, such as candidiasis. In patients who present at the ulcerative stage, it is important to consider other causes of genital ulcers (Table 2).

There are multiple ways to confirm the diagnosis of genital herpes. The classic technique is the Tzanck test, which is a slide preparation of a swab sample from an unroofed vesicle in which multinucleated giant cells are present. However, this method has little utility in current practice. In addition, the Tzanck test will not help to distinguish between HSV-1 and HSV-2 infections. As noted earlier, this distinction may be important as genital herpes is increasingly more likely to be caused by HSV-1. Currently, the preferred method for determining HSV infection is to culture the unroofed vesicle for the virus. However, the presence of a positive antibody test does not guarantee that the lesion in question was caused by HSV, and thus clinical correlation is always necessary. For example, if the patient suffered from a painless genital ulcer and was found to have positive serology for HSV-2, it does not make clinical sense that the lesion was caused by HSV-2. Knowing that many STDs can be inoculated at 1 setting, it may be that the lesion represents a different infection (e.g., syphilis) and the HSV-2 is from a different location in the genital tract.

The use of these type-specific antibodies has important implications for distinguishing between HSV-1 and HSV-2, thus allowing for identification of patients who may have asymptomatic viral shedding and making it possible for physicians to assist patients in managing the risk of transmission. In addition, the use of this technology is more sensitive than culture, and some prefer it to the standard use of culture for ulcer-based infectious outbreaks. Serology is also particularly helpful in cases where culture was not performed during an active outbreak or when a patient presents with lesions that have already crusted over because culture results are less sensitive in these circumstances as compared with cultures taken during the early phases of an active infection. However, there is a time delay from the onset of lesions until the formation of an antibody response, and thus a patient may be serologically negative during the acute phase of an initial infection. Clinicians may
need to perform both acute and convalescent titers, if clinically indicated.

Because of the low sensitivity rates associated with culture, newer methods have been developed to detect HSV shedding. Although PCR analysis has much higher detection rates, it is cost prohibitive at this time. However, research has revealed that much smaller quantities of viral particles are required for detection using PCR. As an example, HSV culture-positive patients were found to have a viral load 250 times greater than culture-negative patients by use of PCR analysis on the same specimens. Like PCR, direct fluorescence antibody testing is also available but is too costly to use on a regular basis.

• **How is an initial episode of HSV infection treated?**

For initial episodes, there are several underlying principles important to treatment. The first is early initiation of antiviral therapy. All of the medications within this class appear to have equal efficacy; therefore, it is important to consider cost and compliance with dosing schedules in the final decision of which antiviral agent to use. Classically, acyclovir has been prescribed at a dose of 200 mg taken 5 times a day for 7 to 10 days. As an alternative, the same medication can be prescribed at a dose of 400 mg taken 3 times daily, as the less frequent regimen may improve compliance. Other oral antiviral regimens are listed in the Table 3.

After initiating antiviral therapy, it is important to provide adequate analgesia either via topical anesthetic ointments or even systemic narcotic analgesics.
as needed. In addition, superimposed yeast infections of the vulva and/or vagina are common and require treatment as well. In fact, the yeast symptoms may predominate and overshadow the true inciting event as happened with this case patient. Finally, initial episodes with sacral nerve involvement may affect the autonomic sacral nerves, thus leading to urinary retention. Catheterization may be needed in these circumstances and it should always be a consideration for severe first episodes.

**CASE CONCLUSION**

The patient returns 1 week later for follow-up. From a clinical standpoint, she has markedly improved. Although the culture report is negative for HSV, the clinician is concerned for a falsely negative culture and orders serologic testing. The patient believes that it is coincidental that the original “yeast infection” ran its course and her symptoms improved on antiviral therapy. Upon receiving positive anti-HSV-2 antibody titers several days later, the patient is advised of the risk of infecting current or future sexual partners who are HSV seronegative. She is also advised of her risk of recurrence and, in case she should become pregnant, her risk of transmission to her newborn should she experience a recurrence before or during labor.

### GENITAL HERPES AND PREGNANCY

**CASE 2 PRESENTATION**

A 23-year-old woman who is gravida 1 para 0 at 40 weeks gestation of an uncomplicated pregnancy presents in active labor. In the course of providing routine intake information, the patient reports to the intake nurse that she has felt a tingling sensation in the genital area for the last 2 days. On further questioning, the patient reports that the tingling was preceded by a numb sensation in the same area for 1 day. She cannot recall ever having been told that she had genital herpes, but she does report multiple bouts with cold sores as a teenager. The father of the baby is uninvolved, and the patient has not engaged in intercourse, oral or vaginal, for the past 4 months. She reports that she suspects the father had been promiscuous prior to their break-up.

- **What are the neonatal and maternal risks associated with HSV infection?**

  **Neonatal Risks**

  The most serious of the HSV sequelae is neonatal HSV infection. Neonatal infection can be localized to 1 of several sites, such as the skin, eye, and mouth. Localized infection is the most frequent presentation, which causes a generally mild illness. Localized disease can progress to encephalitis, with a mortality rate of 15%, or to disseminated disease, with a mortality rate of 57%. Morbidity in surviving infants can be lifelong. In the United States, 2000 newborns contract neonatal herpes each year. Although outcomes of infected neonates have improved with high-dose, longer duration (21 days) antiviral therapy, the outcome remains poor, and prevention of maternal-neonatal transmission offers the

### Table 3. Treatment Options for Genital Herpes

<table>
<thead>
<tr>
<th>First episode</th>
<th>Drugs of choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir 400 mg oral 3 times daily for 7–10 days</td>
<td></td>
</tr>
<tr>
<td>Famciclovir 250 mg oral 3 times daily for 7–10 days</td>
<td></td>
</tr>
<tr>
<td>Valacyclovir 1 g oral twice daily for 7–10 days</td>
<td></td>
</tr>
<tr>
<td>Alternatives</td>
<td></td>
</tr>
<tr>
<td>Acyclovir 200 mg oral 5 times daily for 7–10 days</td>
<td></td>
</tr>
<tr>
<td>Severe (hospitalized patients)</td>
<td>Drug of choice</td>
</tr>
<tr>
<td>Acyclovir 5–10 mg/kg IV every 8 hours for 5–7 days</td>
<td></td>
</tr>
<tr>
<td>Suppression of recurrences*</td>
<td>Drugs of choice</td>
</tr>
<tr>
<td>Acyclovir 400 mg oral twice daily</td>
<td></td>
</tr>
<tr>
<td>Famciclovir 250 mg oral twice daily</td>
<td></td>
</tr>
<tr>
<td>Valacyclovir 500 mg to 1 g once daily†</td>
<td></td>
</tr>
<tr>
<td>Alternatives</td>
<td></td>
</tr>
<tr>
<td>Acyclovir 200 mg oral 2–5 times daily</td>
<td></td>
</tr>
<tr>
<td>Episodic treatment of recurrences‡</td>
<td>Drugs of choice</td>
</tr>
<tr>
<td>Acyclovir 800 mg 3 times daily for 2 days or 400 mg oral 3 times daily for 3–5 days§</td>
<td></td>
</tr>
<tr>
<td>Famciclovir 125 mg oral twice daily for 3–5 days§</td>
<td></td>
</tr>
<tr>
<td>Valacyclovir 500 mg oral twice daily for 3 days</td>
<td></td>
</tr>
</tbody>
</table>


*Some medical letter consultants discontinue preventive treatment for 1–2 months once a year to reassess the frequency of recurrence.

†Use 500 mg once daily in patients with < 10 recurrences per year and 500 mg twice daily or 1 g daily in patients with ≥ 10 recurrences per year.

‡Antiviral therapy is variably effective for episodic treatment of recurrences; only effective if started early.

§No published data are available to support 3-day course.
greatest potential for reducing this serious complication of HSV infection.\textsuperscript{50}

**Maternal Risks**

In rare cases, HSV may present during pregnancy as disseminated, severe infection in the mother. Disseminated HSV can cause hepatitis, pneumonitis, meningitis, encephalitis, and postpartum endometritis. Disseminated HSV usually presents in the third trimester as flu-like symptoms with or without skin lesions characteristic of herpes. In 25\% of cases, the diagnosis is reached only at autopsy.\textsuperscript{31} Viral encephalitis should be considered in any mother with headaches, fever, new-onset seizures, and mental status changes. The diagnosis is made by cerebrospinal fluid PCR assay for HSV.\textsuperscript{32} Herpes endometritis should be considered in parturients with persistent fever after antibiotics, and anticoagulation should be tested by PCR or culture of endometrial biopsy material.\textsuperscript{33} In such cases of disseminated HSV, prompt diagnosis and initiation of antiviral and supportive therapy are essential to clinical outcome.

- **How is HSV transmitted to the neonate?**

**Transmission**

Most newborns acquire the infection in the perinatal period from contact with infected maternal cervicovaginal secretions.\textsuperscript{34} Acquisition risk appears to be the highest when there is a first-episode HSV infection in the third trimester. Risk is also elevated with invasive fetal monitoring that interrupts the neonatal integument, delivery before 38 weeks, and maternal age younger than 21 years.\textsuperscript{35} Given these risk factors for perinatal transmission, precise identification of mothers actively shedding virus could potentially eliminate neonatal herpes.

A very small minority of pregnancies are affected by HSV acquisition remote from delivery. In a prospective study by Brown and colleagues\textsuperscript{35} of 7046 pregnancies at risk for HSV acquisition, 94 (~2\%) women underwent seroconversion during the course of pregnancy, with an equal distribution in each trimester. Among the infants of these women who became HSV seropositive prior to labor, there were no cases of neonatal herpes or any increase in pregnancy-related morbidity. Among the infants born to 9 women who acquired HSV infection at or near the time of labor, neonatal HSV developed in 4, of whom 1 died and 1 had long-term neurologic sequelae. The absence of definable morbidity with HSV seroconversion before the onset of labor in this carefully conducted study must be viewed in light of previous studies demonstrating an association between first episodes of genital HSV infection and preterm labor, intrauterine growth retardation, and spontaneous abortion. Because there was an overall low rate of pregnancy complications in the study, the authors suggest that HSV may have some effect on pregnancy that could be demonstrated only by larger cohort studies and that certain highly symptomatic women or women with evidence of disseminated infection, both of which were underrepresented in their study, may require antiviral chemotherapy.\textsuperscript{35}

- **How should pregnant patients with HSV be managed to prevent neonatal transmission?**

**Prophylaxis Recommendations**

Based on the limited available data, the American College of Obstetrics and Gynecology (ACOG) recommends that women with primary HSV in pregnancy receive acyclovir (or equivalent therapy), 400 mg 3 times daily for 7 to 14 days. When these women reach 36 weeks gestation, they should receive daily suppressive acyclovir (or equivalent) therapy, 400 mg twice daily until delivery; women with first-episode HSV and active genital lesions should undergo cesarean delivery.\textsuperscript{36} Based on consensus or expert opinion, ACOG recommends that all women at risk for recurrent HSV beyond 36 weeks receive acyclovir or equivalent suppressive therapy until delivery and that cesarean delivery be performed only on those women with recurrent HSV who demonstrate active genital lesions or prodromal symptoms during labor (see Figure 3 on page 7).\textsuperscript{36} It should be noted that in women with premature rupture of membranes, cesarean section is not as effective for preventing HSV infection.\textsuperscript{36}

Even rigorous adherence to these practices will not eliminate all cases of neonatal herpes because of the large percentage of women with prior or third trimester primary HSV infections that are asymptomatic and, thus, unrecognized. Studies are underway or awaiting confirmation that test methods to detect women at risk for primary or nonprimary first episode HSV during pregnancy. Such women, if identified, are candidates for prophylactic measures in the third trimester.\textsuperscript{37,38}

**CASE 2 CONTINUED**

The obstetrician suspects that the patient may be experiencing a subclinical nonprimary first episode of genital herpes. Based on these suspicions, the patient is examined for typical vulvovaginal and cervical blisters as well as any atypical ulcers, excoriations, or rashes, but none are identified. The patient is diagnosed with prodromal symptoms without active lesions. Cervical
examination reveals 4-cm of dilatated, intact membranes. The patient’s contractions are becoming more painful. Due to concern that the patient may be actively shedding viral particles, the patient undergoes cesarean delivery. The infant’s clinical course is uncomplicated, and both the mother and infant are discharged on postoperative day 3.

Discussion

Abdominal delivery is the correct choice of delivery route in this patient, as the likelihood of viral shedding is not insignificant. In the past, abdominal delivery was only recommended upon finding physical evidence of recurrence (e.g., blisters of encrusted ulcers). Recent evidence of viral shedding prior to lesion eruption and the recognition that up to 40% of patients present without typical lesions indicates abdominal delivery in this case.37

FUTURE DIRECTIONS

Several new management strategies for genital herpes are close to universal acceptance and merit discussion. The use of PCR for detecting HSV-2 has proved significantly more sensitive than traditional viral culture. In a prospective study comparing culture to PCR, 26% of symptomatic women had HSV detected by culture from at least 1 genital specimen while 46% had HSV detected by PCR.37 During the same period, 0.5% of asymptomatic women had HSV detected by culture, whereas 2.7% asymptomatic women had HSV detected by PCR. Importantly, PCR demonstrated that the number of viral copies of HSV (viral load) detected in genital secretions of asymptomatic women by PCR was often as high as the amount detected in women with genital lesions, although the median amount of HSV DNA detected was greater in women with lesions.15 Although PCR clearly has the ability to detect a higher percentage of asymptomatic disease, it is equally as clear that a substantial number of delivering infants will still be exposed to virus. Expert opinion at present indicates that HSV type-specific PCR is the detection method of choice in centers where the test is available.37

Chemoprophylactic agents play a key role in current HIV prevention trials that aim to assess the role of suppression of HSV-2 infection on the risk for HIV acquisition and transmission.39 An added clinical benefit of treating coinfected individuals is the potential survival benefit as suggested by earlier studies and by the recent findings that HSV-2/HIV dually infected individuals have higher HIV viral loads. Presently, however, there is no consensus on the acyclovir treatment of dually infected patients, and some suggest that treatment may not affect the course of HIV infection.25

SUMMARY

- HSV-1 and HSV-2 share an overall 50% sequence homology throughout the entire genome, and most of the proteins of 1 type are antigenically related to the other, which allows for the partial degree of protection that exposure to 1 type affords to the other type. There are, however, several type-specific regions that may provide opportunity to distinguish the 2 types diagnostically and, potentially, therapeutically.
- Viral particles infect sensory and autonomic nerve endings. Infection of neuronal cells does not always result in cell death. In surviving neurons, the virus transcribes only a limited set of proteins, maintained in a repressed or latent state in which the host neuron is fully functional.
- Seropositive sexual partners of at-risk seronegative persons are frequently shedding virus particles in the absence of symptoms and are thus infectious.
- The preferred method for evaluating HSV infection is to culture the unroofed vesicle for the virus. However, serology has also proven to be efficacious without undue cost.
- For initial episodes, treatment should focus on initiating antiviral therapy and providing adequate analgesia, either via topical anesthetic ointments or even systemic narcotic analgesics as needed.
- The most devastating sequela of herpes genitalis is neonatal herpes infection. Less devastating but similarly important to public health are recurrent infection and the increased risk of HIV transmission in HSV seropositive patients.
- ACOG recommends that women with primary HSV in pregnancy receive acyclovir (or equivalent therapy), 400 mg 3 times daily for 7 to 14 days. At 36 weeks gestation, these women should receive daily suppressive acyclovir (or equivalent) therapy, 400 mg twice daily until delivery, and women with first-episode HSV and active genital lesions should undergo cesarean delivery. Based on consensus or expert opinion, ACOG recommends that women at risk for recurrent HSV beyond 36 weeks receive acyclovir or equivalent suppressive therapy until delivery and that cesarean delivery be performed only on those women with recurrent HSV who demonstrate active genital lesions or prodromal symptoms during labor.
REFERENCES


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