GENITAL HERPES

Diagnosing and Treating Genital Herpes Infection
Case Study and Commentary, Michael F. Rein, MD

INSTRUCTIONS
The following article, “Diagnosing and Treating Genital Herpes Infection,” is a continuing medical education (CME) article. To earn credit, read the article and complete the CME evaluation form on page 703.

OBJECTIVES
After participating in the continuing education activity, primary care physicians should be able to:
1. Be familiar with the classic and other common presentations of genital herpes
2. Recognize the role of herpes simplex virus type 1 in genital infections
3. Understand the value of culture, nonculture viral identification, and serodiagnosis in management
4. Understand the frequency and epidemiologic significance of asymptomatic shedding
5. Know therapeutic options for initial and recurrent disease

Genital lesions are a common presenting complaint among sexually active patients. Although the genital skin is subject to many of the same conditions that affect other areas of the body, sexually transmitted infections assume special importance in the differential diagnosis of genital lesions. The most common causes of genital lesions in the United States in order of frequency are herpes simplex virus (HSV), primary syphilis, and chancroid [1]. Of these, herpes is by far the most frequently occurring infection, although its true incidence is difficult to assess because the disease is not reportable and most infections are subclinical. Seroprevalence studies suggest that approximately 20% of people in the United States are infected with HSV-2 [2,3]. Chancroid had become more common in the United States [4,5], particularly in major metropolitan areas and in the context of sexual contact with prostitutes, but its incidence has recently decreased [3]. Although syphilis has become far less common in the United States, its incidence has recently increased among men who have sex with men [6]. The Centers for Disease Control and Prevention (CDC) have recently undertaken a campaign to eliminate the disease in this country; that is, to reduce the number of new cases annually to fewer than 1000 [7].

Patients with HSV infection often present to a primary care physician. The initial challenge is the differential diagnosis of ulcerative genital disease [1] and the consideration of genital herpes in atypical presentations. The next challenge is to provide nonjudgmental, accurate counseling regarding prognosis, transmissibility, complications, and therapeutic options. Because the social and psychological consequences of genital herpes often dramatically outweigh the medical consequences, patient counseling upon diagnosis is an important component of management. Evidence from the literature can be used cautiously to provide general guidance and assurance to patients diagnosed with HSV infection.

CASE STUDY
Initial Presentation
A 24-year-old woman presents to a physician with 48 hours of genital discomfort and rash.

History
Twenty-four hours before presentation, the patient noted the onset of itching around her introitus. She has seen some blisters and sores, which have become quite painful. She has also felt feverish, and she complains of a relatively severe, nonthrob'ing headache, which is more severe at the back of her head and neck. She has marked discomfort on urinating and says that the discomfort feels both internal and external.

The patient has been married for 4 years and has been monogamous with her husband. She says, somewhat defensively, that she is certain that he has been monogamous as well. She takes oral contraceptives, and has taken the same regimen for 5 years. She does not douche. Cervical cytology, obtained annually, has been normal. She has not started taking newly prescribed or over-the-counter medications and has used no topical preparations. She had sex with 2 partners before marriage, and she believes that her husband had premarital sex with several women. She has never before had genital symptoms except for a single episode of vulvovaginal candidiasis following a course of oral ampicillin for a dental infection 3 years ago. Her periods have been regular and normal for her. There is no prior history of sexually transmitted diseases.

From the Division of Infectious Diseases, University of Virginia Health System, Charlottesville, VA.
Her last sexual contact with her husband was 6 days previously and included cunnilingus. He is asymptomatic.

**Physical Examination**

On examination of the external genitalia, there are clusters of 2-mm vesicles over the labia minora. Some of these appear umbilicated. Many appear to have ruptured to form shallow ulcers, also in clusters. One such cluster surrounds her urethral orifice. The ulcers appear clean, and all are approximately the same size. They are not indurated. There is very mild tenderness over the inguinal nodes bilaterally. The nodes are slightly enlarged but are not fluctuant. The speculum cannot be inserted because of marked introital tenderness.

- **How is symptomatic HSV infection distinguished from other causes of genital lesions?**

**Clinical Features of HSV Infection**

The initial clue to the differential diagnosis of genital lesions lies in the general morphology of the lesions (Table 1). In this patient, however, the diagnosis is not in doubt. Her presentation is typical for genital HSV infection, which can be diagnosed clinically when the presentation is classic. The clinical diagnosis is usually made by observing grouped lesions on an inflammatory base. The vesicles are sometimes observed to be umbilicated. One is more likely to find ulcers rather than vesicles initially in women. The vagina is usually spared in adults (3% to 4% of cases), and the cervix is often involved in primary disease (70% to 90% of cases) [8,9]. Inguinal adenopathy usually develops toward the end of the first week of symptoms (versus chancreid, in which lesions and adenopathy appear at almost the same time). Also supporting the diagnosis of genital herpes in this patient is the incubation period, which is usually 3 to 13 days, with a mean of approximately 6 days [8,9]. In herpetic infection, the lesions are initially vesicular, clean, and all the same size, characteristics that argue convincingly against chancroid [1,10]. Genital zoster is an uncommon condition, with a distribution that is usually unilateral. Fixed drug eruptions produce ulcerations often limited to the genital tract, but these are seen in connection with the use of a new drug, often a tetracycline or sulfonamide, and this patient has no history of such exposure [11,12].

Often, however, the clinical diagnosis of HSV infection can be misleading because many infected patients have atypical or confusing presentations. For example, patients with chancroid may have small ulcers and inguinal adenopathy that invite confusion with HSV infection, and some patients with HSV present with lesions that are primarily papular rather than vesicular or ulcerative. Lesions of herpes can appear in extragenital locations, particularly on the buttocks [13]. Only about 20% of patients who acquire genital herpes manifest the classic clinical picture [14], and another 20% never develop clinical manifestations at all. Thus, about 60% develop atypical and usually mild symptoms that do not suggest the diagnosis. The CDC notes the lack of sensitivity and specificity of the clinical findings in herpes infection [15], an observation that has been confirmed by others [1,16]. Because of the low rate of patients with genital herpes who present with classic findings, a negative physical examination cannot rule out infection [14,17].

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**Table 1. Common Morphologic Presentations of Genital Lesions**

<table>
<thead>
<tr>
<th>Ulcers</th>
<th>Herpes</th>
<th>Chancroid</th>
<th>Syphilis</th>
<th>Trauma</th>
<th>Fixed drug eruption</th>
<th>Lymphogranuloma venereum</th>
<th>Donovanosis (granuloma inguinale)</th>
<th>Behçet’s syndrome</th>
<th>Malignancy</th>
<th>Trichomoniasis</th>
<th>Candidiasis</th>
<th>Histoplasmosis</th>
<th>Mycobacterial infection</th>
<th>Amebiasis</th>
<th>Gonorrhea (rare)</th>
<th>Tularemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vesicles</td>
<td>Scabies</td>
<td>Herpes</td>
<td>Diffuse erythema</td>
<td>Candidiasis</td>
<td>Trauma</td>
<td>Contact dermatitis</td>
<td>Fixed drug eruption</td>
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<tr>
<td>Crusts</td>
<td>Herpes</td>
<td>Scabies</td>
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<tr>
<td>Papules</td>
<td>Venerel warts</td>
<td>Scabies</td>
<td>(moist papules, often crusted)</td>
<td>Molluscum contagiosum (umbilicated)</td>
<td>Candidiasis (satellite lesions)</td>
<td>Syphilis (secondary)</td>
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</tbody>
</table>

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[8,9] References to the original sources are omitted for brevity.
• How is the diagnosis of HSV confirmed?

**Viral Culture**

HSV can be isolated from fresh lesions by standard tissue culture techniques, and viral culture would certainly be positive in a correctly obtained and processed specimen in this case. However, the sensitivity of the culture declines rapidly over the duration of an initial infection, falling to approximately 70% for lesions that have reached the ulcer stage, and is relatively lower in recurrent disease [14]. Had the patient presented a few days later, the culture would have been less trustworthy.

Because of the limitations of viral cultures, there recently has been considerable interest in HSV antigen detection tests using direct immunofluorescence (DFA) and enzyme-linked immunosorbent assays (ELISA). Data are limited on the sensitivity and specificity of these tests, but they probably are between 70% and 90% [17,18]. Newer tests employ the polymerase chain reaction (PCR) to detect viral DNA and provide a specificity reported to be 100% and a sensitivity that is incompletely defined but is higher than that of any other technique [17–19].

• Should any testing be done in this patient?

An advantage to the use of these diagnostic techniques even when the diagnosis is not in doubt is that it allows the clinician to differentiate between HSV-1 and HSV-2. Up to 30% of genital herpes is caused by HSV-1, the type usually associated with lesions of the mouth and lips [8,15]. However, in certain recently studied populations, including younger college students, the fraction of genital herpes caused by HSV-1 is as high as 70%. Knowing which type of virus is present permits more accurate patient counseling since the recurrence rates for HSV-2 and HSV-1 are different, with HSV-2 recurring more frequently. As this woman has had both penile-vaginal and oral-vaginal contact with her husband (and perhaps with previous partners), there is a high likelihood of genital infection with HSV-1, and a test to define viral type is recommended [15].

This woman has initial genital herpes infection, which is a first episode of symptomatic genital infection. True primary herpes is defined as initial genital infection occurring in a patient with no prior infection with either HSV-1 or HSV-2. This differentiation between nonprimary initial and true primary infection is thus made by determining the presence of antibodies to HSV in the patient’s serum. One cannot reliably differentiate the 2 conditions on clinical grounds. However, serologic differentiation of initial from true primary infection is not routinely performed. If she had given a reliable history of orolabial herpes, one might conclude that she is having a nonprimary initial rather than a true primary outbreak. True primary outbreaks tend to be more severe than initial outbreaks.

• What is the significance of headache in this patient?

The headache in the case patient is concerning. Headache, stiff neck, and photophobia have been reported in approximately one third of women with primary infection [8]. Six percent of women with primary HSV infection develop frank, symptomatic aseptic meningitis (without encephalitis) that requires hospitalization. Because mild aseptic meningitis is self-limited and without sequelae, examination of the cerebrospinal fluid is not warranted at this time, and symptoms may be expected to resolve over the next several days [20].

**Diagnosis**

The physician obtains a specimen for culture for herpes virus from a freshly unroofed vesicle that is sent for identification and typing. On concluding the exam, the physician tells the patient that she has genital herpes, and she responds with considerable agitation and anger. She tearfully asks how she could have gotten this infection from her husband, if the diagnosis means that he has been unfaithful to her, and what the diagnosis means for their future sexual relations and her childbearing.

• What can one tell the patient about the epidemiology and consequences of her infection?

**Patient Counseling Issues**

**Source of Infection**

More than half of the persons who acquire genital herpes develop atypical and usually mild symptoms that do not suggest the diagnosis, and an additional 20% remain asymptomatic. Most of these patients can, in fact, be trained to recognize atypical recurrences by correlating the presence of symptoms with positive genital cultures for HSV [21]. Studies suggest that patients who are never symptomatic and those who are intermittently symptomatic but currently without symptoms shed virus about 3% of the time [21]. Among monogamous but regularly sexually active couples who have unprotected sexual contact only when the partner with genital herpes is asymptomatic, the rate of transmission to the other partner is estimated to be 10% per year [22].
Thus, monogamous partners may be in a long-term relationship before the other partner develops genital HSV. These data allow the clinician to suggest that the patient’s husband is likely to have acquired asymptomatic infection before they were married, and that transmission may have occurred only now even though the couple has been regularly sexually active without the use of barrier contraception. Although perhaps comforting, this theory does not obviate the need to evaluate the patient and her husband for other sexually transmitted diseases, perhaps more recently acquired.

The likelihood that one will develop symptomatic rather than asymptomatic disease may be due in part to the genetic makeup of the host and presumably to the virulence of the virus. The development of symptomatic disease appears to be associated with carriage of the major histocompatibility antigen HLA-B27, whereas asymptomatic infection is more likely associated with HLA-Cw2 [23]. If these early observations are confirmed, it may help to explain how an asymptomatic infected individual can transmit infection that is clinically dramatic.

A far less likely scenario is that the patient acquired genital herpes some time in the past and has only now become symptomatic. If this is an important question, it may be addressed by obtaining a serologic test for type-specific antibodies to HSV-1 and HSV-2. Such tests are commercially available. Antibodies usually develop only after about 14 days of infection. Thus, if she were without antibodies to the viral type identified by culture, one could assume that her present condition is a new rather than a recurrent and thus acquired.

The fact that you have genital herpes does not necessarily mean that your partner had a recent sexual contact with another individual. The approximate risk of transmission to a regular sexual partner when the couple has unprotected sex only when the infected partner is asymptomatic is approximately 10% per year. Thus, monogamous partners may be in a long-term relationship before the other partner develops genital herpes.

Consequences for Future Pregnancy
Chronic genital herpes is not a contraindication to pregnancy. Pregnancy does pose potential problems for mother and baby, and management remains somewhat controversial [26]. The risk that the newborn will become infected is higher among women who acquire genital herpes near the time of delivery (30% to 50%) than among women with recurrent herpes (< 1%). The likelihood that a completely asymptomatic individual is shedding virus at the time of delivery is probably as low as 3%. Women with a history of genital herpes should be carefully examined for the presence of active lesions, which are considered by many to be an indication for cesarean section [26,27]. Women without such lesions can be delivered vaginally [15,25,26].

For Counseling Patients with Genital Herpes

**Table 2.** Information for Counseling Patients with Genital Herpes

<table>
<thead>
<tr>
<th>Item</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>You are not alone: approximately 20% of Americans older than 30 years of age have HSV-2 infection.</td>
<td></td>
</tr>
<tr>
<td>Only about 20% of infected individuals have the classical clinical manifestations.</td>
<td></td>
</tr>
<tr>
<td>In patients with symptomatic herpes, 25% of recurrences are asymptomatic, so you can sometimes infect a partner even if you are feeling well.</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic individuals appear to shed virus 3% to 7% of the time, so you could have contracted herpes from someone who never had any symptoms.</td>
<td></td>
</tr>
<tr>
<td>The fact that you have genital herpes does not necessarily mean that your partner had a recent sexual contact with another individual.</td>
<td></td>
</tr>
<tr>
<td>The approximate risk of transmission to a regular sexual partner when the couple has unprotected sex only when the infected partner is asymptomatic is approximately 10% per year.</td>
<td></td>
</tr>
<tr>
<td>The median number of recurrences with HSV-2 infection during the first 3 to 4 years is about 5 per year. There are fewer recurrences per year on average with HSV-1 infection.</td>
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<tr>
<td>The number of recurrences does decrease over time.</td>
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</tbody>
</table>

- Should the patient be assessed for other sexually transmitted diseases?

Because of the possibility that this infection actually represents an extramarital contact by the patient or her husband,
she should be asked to return when she is less symptomatic so that she can be evaluated for coincident infections, notably gonorrhea, chlamydial infection, trichomoniasis, and bacterial vaginosis [27,28].

• What agents are used to treat initial HSV infection?

Therapy for Initial Infection
Several drugs are effective for the treatment of initial genital herpes. The regimens listed in Table 3 are recommended by the CDC. One may expect the systemic symptoms and the formation of new lesions to cease within 48 hours of initiating therapy, and the duration of symptoms to be reduced [27]. Valacyclovir (Valtrex), an acyclovir prodrug, and acyclovir (Zovirax) are equally effective, but valacyclovir offers a more convenient dosing schedule. Famciclovir (Famvir) is a penciclovir prodrug, and penciclovir has a longer intracellular half-life than does acyclovir; however, unlike acyclovir, it is not an obligate DNA chain terminator and is therefore a less potent inhibitor of herpetic DNA polymerase, which is the mechanism of action for all of these drugs. The 3 drugs are essentially clinically equivalent.

Management and Follow-up
The physician provides counseling to the patient, addressing her concerns about how she may have become infected and how the infection may impact sexual relations with her husband and childbearing. He gives the patient a prescription for acyclovir 400 mg 3 times daily for 10 days and asks her to return in 2 weeks.

The patient returns 2 weeks later feeling much improved. Her vulvar discomfort has decreased and her headache has resolved. No new vesicles are observed, and the existing lesions have crust over. The culture obtained at her initial visit is positive for HSV and has been typed as HSV-2. Examination for other sexually transmitted infections is performed and is negative. The patient is concerned about recurrences. The physician asks her to return immediately if she develops genial symptoms, including unusual itching or tingling.

• How are episodes of recurrent disease treated?

Recurrent Disease
Within the first year after infection, recurrences are seen in approximately 90% of symptomatic patients infected with HSV-2 but in only 25% to 50% of those infected with HSV-1 [29]. Most patients with HSV-2 infection who have symptomatic recurrences experience about 4 to 8 per year, but the frequency of recurrence varies dramatically from patient to patient. The median number of yearly recurrences during the first 3 to 4 years is approximately 5 [29]. Recurrences with HSV-1 are on average nearly 10 times less frequent [29–31]. Recurrences proceed through the same stages as primary disease, but they are far milder than the initial episode and they generally last only 6 to 10 days. Recurrent disease may be preceded by a prodrome of itching, tingling, or burning that begins 6 to 24 hours before lesions appear [8]. This is an important finding because suppressive therapy begun during the prodrome has a high likelihood of aborting the recurrence. The rate of recurrence of genital herpes diminishes gradually over years [29].

Equivalent regimens for recurrent disease recommended by the CDC are shown in Table 3. There is recent interest in shorter courses of therapy for recurrences. Based on a study of 131 people with recurrent genital herpes (type 2), acyclovir 800 mg orally 3 times daily for 2 days reduced the duration of lesions from 6 days to 4 days [30]. A 3-day course of valacyclovir 500 mg twice daily was found to be as effective as a 5-day course of the same regimen in 800 patients; the length of a recurrent episode was 4.7 days with the shorter course compared to 4.4 days with the longer course [31].

It should be noted that the effect of treatment on episodes of recurrent disease is not dramatic. Many patients have such mild recurrences that they do not bother to take medication.

Table 3. Recommended Treatment for Genital Herpes

<table>
<thead>
<tr>
<th>Initial infection</th>
<th>7 to 10 days of oral therapy with one of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir 400 mg 3 times daily</td>
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<tr>
<td>Acyclovir 200 mg 5 times daily*</td>
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<tr>
<td>Famciclovir 250 mg 3 times daily</td>
<td></td>
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<tr>
<td>Valacyclovir 1 g twice daily*</td>
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</table>

<table>
<thead>
<tr>
<th>Recurrent disease</th>
<th>Acyclovir 400 mg orally 3 times a day for 5 days</th>
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<tbody>
<tr>
<td>Acyclovir 200 mg orally 5 times a day for 5 days*</td>
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</tr>
<tr>
<td>Acyclovir 800 mg orally twice daily for 5 days</td>
<td></td>
</tr>
<tr>
<td>Famciclovir 125 mg orally twice daily for 5 days*</td>
<td></td>
</tr>
<tr>
<td>Valacyclovir 500 mg orally twice daily for 3 to 5* days</td>
<td></td>
</tr>
<tr>
<td>Valacyclovir 1 g orally once daily for 5 days</td>
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<table>
<thead>
<tr>
<th>Suppression of frequently recurring genital herpes</th>
<th>Acyclovir 400 mg orally twice daily</th>
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<tbody>
<tr>
<td>Famciclovir 250 mg orally twice daily</td>
<td></td>
</tr>
<tr>
<td>Valacyclovir 500 mg orally once daily</td>
<td></td>
</tr>
<tr>
<td>Valacyclovir 1 g orally once daily</td>
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*Regimen indicated by package insert.
Further Follow-up

The patient returns 3 weeks later with a complaint of genital discomfort of 12 hours’ duration. She is afebrile and does not have a headache. She is observed to have a single labial vesicle. She is diagnosed with recurrent disease and is given a prescription for acyclovir 400 mg 3 times daily for 5 days.

The patient continues to suffer symptomatic recurrences every 3 to 4 weeks. Each of the recurrences is preceded by a prodrome of paraesthesias for about 24 hours before the appearance of lesions [8]. These recurrences are sufficiently severe to interfere with sexual activity and with work. She asks for help.

- When is chronic suppressive therapy used?
- What new therapies are being explored?

For patients with frequent recurrences, continuous therapy with an antiviral agent often provides considerable relief. Suppressive therapy not only reduces the frequency of symptomatic recurrences, but it also reduces the frequency of (but does not eliminate) asymptomatic shedding [15,34–36]. The regimens for chronic suppression are approximately equivalent (Table 3) [15]. One may expect a reduction in the frequency of recurrences of approximately 70% to 80% with any of these regimens. The safety of acyclovir has been demonstrated in studies extending for 5 years.

There has been recent interest in the immune modifiers imiquimod and resiquimod, which can be applied topically to genital lesions. A recent study has shown that treatment of episodic recurrences with a combination of oral acyclovir and topical resiquimod (not yet available) can dramatically prolong the interval between recurrences [37]. In addition, a vaccine that has been shown to decrease transmission of HSV-2 to women without prior exposure to HSV-1 is under development [38]. The vaccine along with the immune modifiers may be available in the future.

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References


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Part 1. Please respond to each statement.

<table>
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<tr>
<th>Strongly Agree</th>
<th>Strongly Disagree</th>
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I was provided with new information pertinent to my practice. □ □ □ □ □
I reaffirmed a specific skill or knowledge. □ □ □ □ □
This article will help with clinical decision making. □ □ □ □ □
Relevant clinical outcomes are addressed. □ □ □ □ □
The case is communicated in a manner that kept my interest. □ □ □ □ □
The case presentation is realistic and effective. □ □ □ □ □
I could easily interpret the tables and figures. □ □ □ □ □
My attitude about this topic changed in some way. □ □ □ □ □

Additional comments:____________________________________________________________________________________
________________________________________________________________________________________________________

Part 2. Please complete the following sentence.

As a result of reading this case study, I . . .

□ see no need to change my practice.
□ will seek more information before modifying my practice.
□ intend to change the following aspect(s) of my practice: (Briefly describe)
________________________________________________________________________________________________________
________________________________________________________________________________________________________


Signature: ____________________________ Date: ____________________________

Part 4. Identifying information: Please PRINT legibly or type the following:

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