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This Practice Bulletin was developed by the ACOG Committee on Practice Bulletins—Gynecology with the assistance of Anna Wald, MD, and Zane Brown, MD. The information is designed to aid practitioners in making decisions about appropriate obstetric and gynecologic care. These guidelines should not be construed as dictating an exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.

Reaffirmed 2010

Gynecologic Herpes Simplex Virus Infections

Both herpes simplex virus (HSV) type 1 and HSV type 2 can cause genital herpes. Because the infection is chronic, genital herpes has become the most common sexually transmitted disease among women (1). The prevalence of the HSV-2 antibody among women in the United States is 26%, although genital herpes has been diagnosed in only a small proportion (10–25%) of individuals with HSV-2 antibodies (2). Herpes simplex virus type 1 is becoming a more frequent cause of genital herpes, especially among young women (3). Overall, HSV-1 seroprevalence in the United States is estimated at 67%, although serologic data do not provide information about site of infection (4). Recent advances in diagnostic methods and therapeutic options are likely to change the management of genital herpes.

Background

Serologic surveys show that 26% of women aged 12 years and older have antibodies to HSV-2. This represents a substantial increase in prevalence since the 1970s and suggests that more than 910,000 new infections with HSV-2 occur annually in women (5). The increase in the HSV-2 seroprevalence has been mirrored by a continual increase in the reported number of cases of first episode genital herpes seen in physician offices, with approximately 150,000 cases reported in 2000 (6). Correlates of HSV-2 antibodies include markers of high levels of sexual activity, such as reported number of sexual partners and age of first sexual contact (7). However, these risk factors do not reliably identify women with HSV-2 because the infection has reached such high levels that even women without these risk factors may be HSV-2 seropositive.

The reported HSV-2 seroprevalence underestimates the frequency of genital herpes because an increasing proportion of first episode genital herpes is caused by HSV-1 infection (8, 9). Although the initial presentation of genital herpes is the same for HSV-1 and HSV-2, the rate of recurrence is much lower

for HSV-1, and most recurrences are caused by HSV-2 (10). Women with genital HSV-2 will have an average of 4 recurrences in the first year of infection compared with 1 recurrence for genital HSV-1. After the first year, the rate of recurrences decreases very slowly for HSV-2, but recurrences are rare for HSV-1 after the first year of infection. As such, the type of genital herpes has prognostic significance for frequency of recurrences and should be determined in every patient (1). In addition, although the acquisition of a new HSV-1 infection in an individual with HSV-2 antibodies is unusual, women with genital HSV-1 infection are still at risk for HSV-2 acquisition (11).

Genital HSV infection can cause a large spectrum of disease. First episode infections, which represent new acquisition of HSV, usually are most severe, and recurrent infections may be milder (12). However, serologic studies show that up to 25% of first clinical episodes are in reality first recognized recurrences; its presentation often is surprising to the patient and the provider (13, 14). First episode infections often are accompanied by systemic symptoms, including prominent flulike syndrome and frequent neurologic involvement, with aseptic meningitis reported in up to 25% of patients. However, as many as 75% of primary infections are unrecognized by either patient or provider (15). Recurrences usually are limited to the genital area. Most women with HSV-2 do not know they have genital herpes because their recurrences are mild and infrequent (16, 17). Such women may have nonspecific genital conditions and may have been receiving treatment for other genital conditions, such as recurrent yeast infections, urinary tract infections, or allergic rashes in the genital area (18).

An important feature of HSV infection is intermittent reactivation, with or without accompanying symptoms, and resultant shedding of the virus in the genital tract (19). DNA from HSV can be detected in the genital tract 10–50% of the time among HSV-2 seropositive women (20). Women close to the time of acquisition or with severe clinical disease have a higher risk of viral shedding between symptomatic recurrences (19, 21). For example, in a study of women with genital HSV-2 infection within 2 years of HSV-2 acquisition, HSV-2 was isolated in culture from the genital area on 9.9% of days overall and on 6.9% of days without genital lesion (19). At those times, the virus can be transmitted sexually or perinatally (22). For many patients, the most bothersome aspect of genital herpes is the unpredictable nature of viral shedding.

An accurate diagnosis enables appropriate treatment for the woman with genital herpes. In addition, it can reduce the risk of transmission of HSV to a sexual partner and reduce the risk of HSV transmission to a neonate.

Clinical Considerations and Recommendations

How is the diagnosis established?

It is difficult to make the diagnosis of genital herpes on clinical grounds alone (1). The classic presentation of a painful cluster of vesicles and ulcers occurs in a small proportion of women, and most women will have atypical lesions, such as abrasions, fissures, or itching without obvious lesions. Conversely, even in at-risk women with a presentation compatible with genital herpes, up to 20% of women will not have genital herpes (15). Thus, a definitive diagnosis should be confirmed by a laboratory test, even if the infection was established in the past on clinical grounds.

Traditionally, the laboratory test used most often has been viral culture (23) because it is highly specific, widely available, and relatively inexpensive. Viral culture can be useful in women presenting with new or recurrent genital ulcer disease. However, viral culture is insensitive, even with a primary infection, with a false-negative rate up to 25%. In recurrent disease, the rate of viral isolation is less than 50%. This low rate of viral isolation results in the need for repeat visits or leaves the impression that the patient does not have genital herpes. Antigen detection tests also are available. They have comparable performance characteristics to viral culture but do not distinguish between HSV-1 and HSV-2 infection.

Polymerase chain reaction (PCR) testing has become more available, and several studies have demonstrated that its sensitivity is 1.5–4 times greater than viral culture (24–26). Thus, PCR is the test of choice in the diagnosis of herpes-related infections of the central nervous system (meningitis and encephalitis) (27–29). Because samples for PCR testing are easier to obtain and more stable than samples for viral culture, PCR testing is likely to replace viral culture for the diagnosis of HSV genital infections in the future (30).

In addition to viral detection methods, the detection of type-specific antibodies to HSV-1 and HSV-2 also can help to establish the diagnosis. The incubation period for HSV is short (approximately 4 days), and infection of the ganglia with establishment of latency has occurred by the time the patient is evaluated for symptomatic disease. Antibodies to HSV-2 are detected 2–12 weeks after acquisition of infection and persist indefinitely (31). Only tests that are based on the detection of antibody response to glycoprotein G-2 for HSV-2 and glycoprotein G-1 for HSV-1 are type specific because much of the immune response is type-common for both HSV types. Many serologic tests on the market are not type specific, despite labeling claims to the contrary (32). Currently,

there are only 3 commercially available, FDA-approved type-specific tests (Herpes Select ELISA, Herpes Select Immunoblot, Captia ELISA) for serologic diagnosis of genital herpes, although other tests are in development. When compared with the Western blot test, the sensitivity of these tests range from 96% to 100%, and specificity is 97–98% (31). Caution should be used in populations with low HSV-2 prevalence because the positive predictive value could be low, and a confirmatory test, such as Western blot, may be required. The serologic test results are likely to be negative with newly acquired genital herpes because the median time to seroconversion is 22 days by enzyme-linked immunosorbent assay with approximately 20% still remaining seronegative after 3 months, particularly if the patient has received antiviral chemotherapy (33).

Is there a role for testing an asymptomatic patient who reports possible exposure?

Most women with genital HSV-1 or genital HSV-2 infection are asymptomatic. A small proportion may recall symptoms or lesions compatible with genital herpes when they receive a diagnosis of HSV-2. Because HSV is so prevalent among women, infection rates are very high among sexually active women, even if the number of sexual partners is not very high. Therefore, type-specific antibody testing is more accurate than assessment of infection based on symptoms or past sexual behavior (15). Such testing is especially important in women who are in relationships with partners who have genital herpes. In this setting, knowledge of infection may result in decreased distress because the relationship is no longer discordant, and confirmation of seronegativity may precipitate increased adherence to interventions to reduce transmission.

Is there a role for postexposure prophylaxis in an asymptomatic patient?

No data are available on the efficacy of postexposure prophylaxis in an asymptomatic patient. Chronic or intermittent antiviral therapy is not recommended for women who lack HSV-2 infection and whose partners have HSV-2. However, some physicians offer antiviral therapy in the setting of unanticipated known high-risk exposure (for example, rape or intercourse without a condom with a partner who had an unnoticed recurrence). Although the effectiveness of this approach is unlikely ever to be documented, the safety of antiviral medication for HSV suggests this approach carries very low risk.

How are first clinical episodes of infection treated?

Acyclovir, famciclovir, and valacyclovir are antiviral drugs approved for treatment of genital herpes (1, 34). They interrupt viral DNA synthesis and have excellent safety profiles. They require viral thymidine kinase for the initial activation step; that is, the drug is not activated unless HSV is actively replicating. Comparative trials of these medications suggest they have comparable clinical efficacy and result in a comparable decrease in viral shedding. Because acyclovir is available in generic form, it generally is the least expensive product. Valacyclovir, a prodrug of acyclovir, can be taken less frequently than acyclovir and famciclovir for some indications, which may be an advantage for some patients. Table 1 lists the antiviral regimens recommended for genital herpes in nonpregnant women.

Treatment should be offered for first episodes of genital herpes, even if they appear to be mild initially. Treatment of first episodes of genital herpes decreases lesions, viral shedding, and symptoms but does not affect the long-term natural history of the infection (35). Newly acquired HSV infections can have a prolonged course, with systemic and neurologic involvement that can be substantially ameliorated by using antiviral therapy (36). Oral therapy is recommended, except in severe cases in which a woman is unable to tolerate oral intake or has prominent neurologic involvement. Such patients should be hospitalized and treated with intravenous acyclovir. Topical antiviral medication is not effective therapy and does not add to the benefit of the oral medication; its use is discouraged.

Antiviral medication is the best intervention for severe symptoms. In addition, analgesics should be provided as needed (ie, acetaminophen or ibuprofen). Warm water baths often are helpful during the first few days. Topical lidocaine also is occasionally beneficial, but it can result in local allergic reactions.

How are recurrent episodes treated?

Recurrent episodes of genital herpes can be managed effectively either with daily suppressive or episodic antiviral drugs. The choice of approach should be made in consultation with the patient; the frequency of recurrences should be one, but not the only, consideration in deciding whether to use suppressive therapy.

When is treatment to prevent recurrence indicated, and which regimens are effective?

Episodic therapy decreases the duration of the episode (lesion, pain, and viral shedding) and is most effective when the patient initiates the therapy at prodrome or at

the beginning of the episode. This form of therapy is most effective for a patient with infrequent symptomatic recurrences. Therefore, women who choose this approach should be encouraged to fill their prescriptions and have the medications available.

Suppressive therapy (in which the medication is taken daily) for genital herpes prevents approximately 80% of recurrences. Studies indicate many patients prefer this treatment (37, 38). Breakthrough recurrences are short, and in some patients, this approach may eliminate recurrences for several years. In those taking daily antiviral therapy, viral shedding from the genital area is markedly decreased, and the breakthrough shedding contains reduced amounts of viral DNA (21). This reduction in shedding translates into a 48% reduction in transmission between sexual partners (39).

How are severe episodes treated?

Some patients have severe disease or complications, such as disseminated infection, pneumonitis, hepatitis, or complications of the central nervous system (eg, meningitis, encephalitis), that require hospitalization. They should receive intravenous acyclovir therapy (see Table 1) (1).

How should patients be counseled about living with genital herpes?

Management of women with genital herpes may be complicated by psychologic distress, especially at the time of initial diagnosis (40). Counseling them about the disease may decrease the distress (41). Therefore, women who present with a first clinical episode of genital herpes and are overwhelmed by the diagnosis and the clinical illness may require a separate visit for counseling. Many materials, both printed and web-based, are available to complement counseling, and their use is encouraged.

Women in whom a first episode genital HSV infection is diagnosed should be told they are likely to have recurrences and that these will be milder than the first episode. Women without a history of genital herpes are

Table 1. Recommended Antiviral Regimens for Genital Herpes

Indication	Drug	Dose	Duration of Therapy
First episode of genital herpes	Acyclovir	400 mg PO tid	7–10 d; longer if new lesions persist
	Acyclovir	200 mg PO 5 times per day	
	Valacyclovir	1,000 mg PO bid	
	Famciclovir	250 mg PO tid	
Recurrent genital herpes			
Episodic therapy	Acyclovir	400 mg PO tid	5 d
	Acyclovir	200 mg PO 5 times per day	5 d
	Acyclovir	800 mg PO bid	2 d*
	Valacyclovir	500 mg PO bid	3–5 d
	Valacyclovir	1,000 mg PO sid	5 d
	Famciclovir	125 mg PO bid	5 d
Suppressive therapy	Acyclovir	400 mg PO bid	Suppressive therapy can be continued for several years†
	Valacyclovir	500–1,000 mg PO sid	
	Famciclovir	250 mg PO bid	
Severe disease/concurrent complications	Acyclovir	5–10 mg/kg of body weight intravenously every 8 h	2–7 d or until clinical improvement is observed, followed by oral antiviral therapy to complete at least 10 days of total therapy

Abbreviations: bid, twice per day; PO, orally; sid, once per day; tid, 3 times per day.

*Thrice-daily acyclovir, 800 mg, has been shown to be effective when given for 2 days (Wald A, Carrell D, Remington M, Kexel E, Zeh J, Corey L. Two-day regimen of acyclovir for treatment of recurrent genital herpes simplex virus type 2 infection. Clin Infect Dis 2002;34:944–8.).

†Annual discussions with patients about continuation are recommended, but the medication does not need to be discontinued. Antiviral resistance has not emerged in immunocompetent individuals (Fife KH, Crumpacker CS, Mertz GJ, Hill EL, Boone GS. Recurrence and resistance patterns of herpes simplex virus following cessation of > or = 6 years of chronic suppression with acyclovir. Acyclovir Study Group. J Infect Dis 1994;169:1338–41.).

Data from Sexually transmitted diseases treatment guidelines 2002. Centers for Disease Control and Prevention. MMWR Recomm Rep 2002;51(RR-6):1–82.

likely to recognize recurrences once they know they have HSV-2 infection. Women should be told they may have viral shedding with or without symptoms and that they are infectious at that time. It is important to reassure women that they can have healthy children despite the infection and that the risk of perinatal transmission of herpes is low if the infection is acquired before or during the first half of pregnancy.

Often, the most difficult part of having genital herpes is telling a partner about the infection. However, this should be encouraged, ideally before the initiation of sexual activity. If the partner is known to have the same type of genital herpes (ie, HSV-1 or HSV-2 concordance), transmission of a different strain of the same type of virus is thought to occur infrequently, and safer sex practices specifically to avoid HSV are not necessary.

What are appropriate methods for preventing the acquisition of genital herpes by women whose partners have genital herpes?

Women who have partners with genital herpes should be tested with type-specific serology to assess the woman's risk of infection. A finding of concordant HSV types may be reassuring to the couple. If the partners have discordant HSV types, the couple should be counseled about consistent use of condoms or dental dams, although condoms do not offer total protection from acquisition of HSV-2 infection (42). If the couple is discordant with the woman being at risk for acquiring genital HSV-1 or HSV-2 from her partner, the risk of new HSV infection during late pregnancy should be explained together with its consequences, such as a 40–50% rate of infection of the newborn (43). Finally, use of suppressive antiviral therapy in the potential source partner has been shown to decrease transmission of HSV-2 by 48% to susceptible partners (39). However, this trial did not evaluate prevention of HSV-1 transmission or transmission of HSV-2 to pregnant women.

A preventive vaccine with recombinant glycoprotein D for genital herpes currently is being developed. In early trials, the vaccine protected seronegative women from genital herpes disease (73% reduction) and showed partial protection from HSV-2 infection (40% reduction) (44). The effect of the vaccine on subclinical shedding in women who acquire HSV-2 after vaccination is unknown. An ongoing trial is evaluating this vaccine in more than 7,000 seronegative young women. The vaccine lacked efficacy in men and in women with previous HSV-1 infection.

Summary of Recommendations

The following recommendations are based on good and consistent scientific evidence (Level A):

- Antiviral therapy should be prescribed at the first clinical episode to reduce the duration of symptoms and viral shedding.
- Women should be offered antiviral treatment for recurrent episodes at prodrome or at the beginning of an episode of genital herpes.
- Women with frequent recurrences should be offered suppressive therapy.
- For couples in which one partner has HSV-2 infection, suppressive antiviral therapy should be recommended for the partner with HSV-2 to reduce the rate of transmission.
- Topical antivirals are not effective in the treatment of genital herpes and should not be used.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- Clinical suspicion of genital herpes should be confirmed using reliable laboratory testing.
- Discordant couples should be counseled that consistent use of condoms decreases but does not eliminate the risk of transmission.

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The MEDLINE database, the Cochrane Library, and ACOG's own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985 and June 2004. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least 1 properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than 1 center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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