CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Genital Herpes

John W. Gnann, Jr., M.D., and Richard J. Whitley, M.D.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

From the Department of Medicine, Division of Infectious Diseases, Medical University of South Carolina, Charleston (J.W.G.); and the Department of Pediatrics, Division of Infectious Diseases, University of Alabama at Birmingham, Birmingham (R.J.W.). Address reprint requests to Dr. Gnann at the Department of Medicine, Division of Infectious Diseases, Medical University of South Carolina, 135 Rutledge Ave., MSC 752, Charleston, SC 29425, or at gnann@musc.edu.

N Engl J Med 2016;375:666-74.
DOI: 10.1056/NEJMcp1603178

An audio version of this article is available at NEJM.org

A 25-year-old woman visits her physician and reports three brief episodes of small, tender, labial ulcerations over the past year. The physical examination is unremarkable. Type-specific herpes simplex virus (HSV) serologic tests are positive for HSV type 1 (HSV-1) and type 2 (HSV-2). The patient is distressed to learn that she has genital herpes, particularly since she has been contemplating pregnancy. Her husband of 2 years reports no history of HSV infection; subsequent testing reveals that he is seropositive for HSV-1 and seronegative for HSV-2. How would you advise this couple?

THE CLINICAL PROBLEM

HSV-1, which is usually transmitted in childhood through nonsexual contact, is the primary cause of orolabial herpes, but it can also cause genital infection. HSV-2, which is usually sexually transmitted, causes genital infection, but it is an uncommon cause of orolabial herpes. HSV-2 seropositivity rates increase in adolescence and young adulthood with the onset of sexual activity and plateau at approximately 30 years of age. In the period from 2005 through 2010 in the United States, the seroprevalence of HSV-1 was 53.9% and the seroprevalence of HSV-2 was 15.7% among persons 14 to 49 years of age.[1] The seroprevalence of HSV-2 had decreased from a rate of 21.2% recorded in the period from 1988 through 1994.[2] Preexisting HSV-1 antibodies provide only partial protection against acquisition of HSV-2.[3]

Rates of HSV-2 infection are highest among women, non-Hispanic blacks, men who have sex with men, and immunocompromised persons (including persons who are seropositive for human immunodeficiency virus [HIV]).[2,4] Genital HSV infection is an important risk factor in HIV transmission.[5] This review will focus on genital HSV disease in immunocompetent patients.

Among Americans who are 14 to 19 years of age, the seroprevalence of HSV-1 has decreased by 30% over the past 30 years; thus, an increasing proportion of adolescents lack protective HSV-1 antibodies when they become sexually active.[1,6] This lack of HSV-1 antibodies has led to an increased frequency of HSV-1 genital herpes acquired from oral–genital sex practices. In some populations (especially young heterosexual women who are 18 to 22 years of age, non-Hispanic whites, and men who have sex with men), HSV-1 is a more common cause of initial episodes of genital herpes than HSV-2.[7,8]

INITIAL GENITAL INFECTION

The clinical presentation of symptomatic initial genital herpes does not differ between HSV-1 and HSV-2 infection.[8] After an incubation period of 4 to 7 days, multiple lesions appear on the genitals (or adjacent skin), usually bilaterally, and

KEY CLINICAL POINTS

GENITAL HERPES

- In some populations, herpes simplex virus (HSV) type 1 (HSV-1) is a more common cause of initial episodes of genital herpes than HSV type 2 (HSV-2).
- The diagnosis of genital herpes is best accomplished with type-specific serologic tests and a polymerase-chain-reaction assay (or viral culture) of lesions.
- Symptomatic episodes of initial or recurrent genital herpes can be effectively treated with antiviral medications (acyclovir, valacyclovir, or famciclovir).
- Asymptomatic shedding of HSV from the genital tract is the most common source of transmission of infection.
- Daily suppressive antiviral therapy significantly reduces the frequency of symptomatic recurrences of genital herpes and asymptomatic viral shedding, and it reduces the risk of transmission of HSV-2 to a susceptible partner by almost 50%.
- All persons with a diagnosis of genital herpes should be offered screening for other sexually transmitted diseases, including human immunodeficiency virus infection.

they progress through stages of erythema, papules, short-lived vesicles, painful ulcers, and crusts that resolve over a period of 2 to 3 weeks (Fig. 1). Approximately half the patients with symptomatic genital lesions report headache, fever, malaise, dysuria, or tender inguinal lymphadenopathy. However, most patients with initial genital herpes do not have conspicuous lesions and systemic symptoms. In one study, 74% of initial genital herpes infections due to HSV-1 and 63% of initial genital herpes infections due to HSV-2 in women were asymptomatic.[8]

The severity of symptoms is greater in patients with primary initial genital herpes (who are seronegative for both HSV types) than in patients with nonprimary initial genital herpes (who have preexisting antibodies against the converse HSV type). Initial HSV-2 genital infection in persons with preexisting HSV-1 antibodies is often asymptomatic.

RECURRENT GENITAL DISEASE

Reactivation of latent HSV infection results in either symptomatic recurrence of genital herpes or asymptomatic viral shedding, which is defined as the presence of infectious HSV on mucosal or skin surfaces that is detectable by means of polymerase-chain-reaction (PCR) assay or culture, without clinical signs or symptoms. Symptomatic recurrences may be preceded by localized prodromal symptoms (e.g., itching or tingling) and are typically less severe than symptomatic initial disease. Lesions are usually unilateral and resolve within 5 to 10 days. Recurrent lesions can be atypical and appear as linear fissures or excoriations. On the basis of clinical examination, it is often impossible to determine definitively whether a first symptomatic episode of genital herpes is initial or recurrent disease, although the presence of a prodrome suggests a recurrence.

Symptomatic reactivations are less frequent with HSV-1 genital infection than with HSV-2 genital infection. Within the first year after initial infection, rates of symptomatic recurrence of HSV-1 genital infection are 20 to 50%, whereas rates of symptomatic recurrence of HSV-2 genital infections are 70 to 90%[9]; the median number of symptomatic recurrences is 1.3 and 4.0, respectively. However, up to 20% of patients have 10 or more recurrences in the first year after initial HSV-2 infection. Recurrences of genital herpes become less frequent over time but continue in many patients for more than 10 years.

Only 10 to 25% of patients with serologically confirmed HSV-2 infection are aware that they have genital herpes.[2,10] Among a large sample of American women who were 18 to 30 years of age and who had no history of HSV infection, seroprevalence rates of HSV-1 were 53% and seroprevalence rates of HSV-2 were 12%; 7% of the patients were dually infected.[11] Persons with undiagnosed HSV-2 infection are the most important source of new transmissions. Transient episodes (often <24 hours) of asymptomatic shedding of infectious virus from multiple genital sites have been detected with the use of PCR in 80 to 90% of HSV-2–seropositive persons.[12] Shedding occurs during 10 to 20% of days, but at unpredictable intervals.[13,14] In any given sexual encounter, the risk of transmission to a susceptible partner is higher when symptomatic genital lesions are present (owing to higher quantities of HSV present with active lesions) than when viral

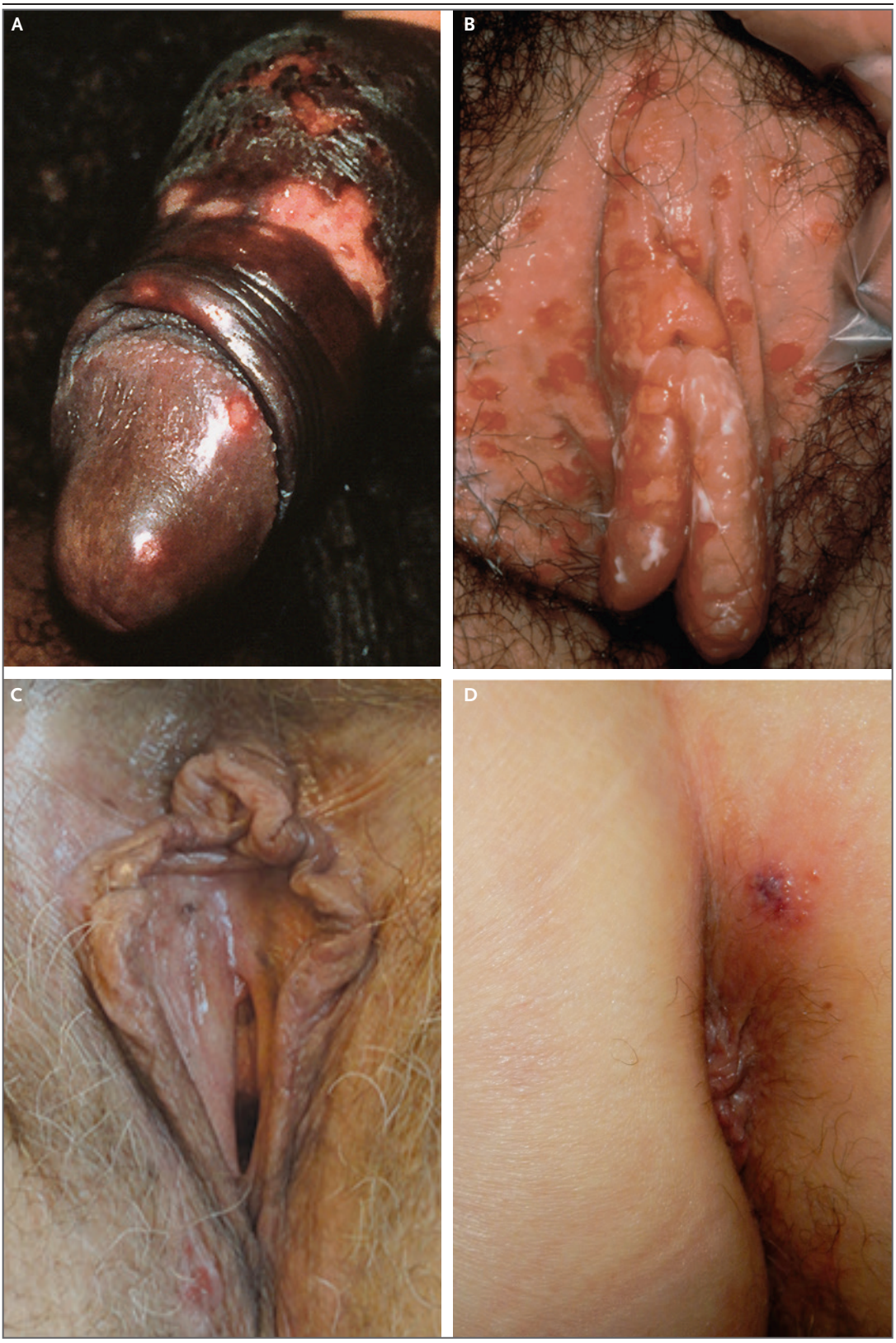

Figure 1 (facing page). Clinical Presentation of Genital Herpes.

Panel A shows multiple ulcerative lesions on the penile glans and shaft in a man with initial herpes simplex virus type 2 infection. Panel B shows multiple labial ulcerations in a woman with genital herpes. Although this is a "classic" presentation of initial genital herpes, in most patients with symptomatic infection, the lesions are fewer and less prominent. Panel C shows genital herpes in a woman with small perineal ulcerations. This is a more typical presentation in which the lesions are more subtle. Panel D shows genital herpes manifesting as perianal lesions. The lesions of genital herpes are often seen outside the genitalia, in the suprapubic, thigh, buttock, and perianal areas. Photographs courtesy of Rajul Patel, F.R.C.P. (Panel B) and Christine Johnston, M.D., M.P.H. (Panels C and D).

shedding is asymptomatic. However, the high frequency of asymptomatic shedding makes it the leading source of new cases.[15]

NEONATAL HSV INFECTION

Infection resulting from vertical transmission of HSV from a mother to an infant is termed "neonatal herpes" and is associated with high morbidity among infants.[16] Transmission most commonly occurs at delivery when the infant comes in contact with maternal genital secretions that contain HSV. In severe cases, multiorgan involvement occurs in the infant, with an associated mortality of 30%.

The risk of transmission is highest (30 to 50%) when primary genital herpes develops in the mother during late pregnancy, when there is no opportunity for transplacental transfer of neutralizing antibodies to the fetus.[17] The risk of transmission is much lower among mothers with recurrent genital herpes who were infected before pregnancy.[17] The risk of vertical transmission is higher with HSV-1 than with HSV-2.[17] Most mothers of babies in whom neonatal herpes develops report no history of symptomatic genital herpes.

STRATEGIES AND EVIDENCE

DIAGNOSIS

The acute onset of multiple painful vesicular or ulcerated lesions in the genital (or perigenital) area of a sexually active person strongly suggests genital herpes, especially if the patient reports recurring lesions (Fig. 1). Laboratory confirmation of the clinical diagnosis is strongly recommended for several reasons. First, lesions may be inconspicuous or atypical, so that clinical diagnosis is unreliable. Second, the distinction must be made between HSV-1 and HSV-2 infection so that an informed discussion of the natural history and prognosis can be initiated. Third, a definitive diagnosis is warranted given the complex social and psychosexual implications of genital herpes. Fourth, an incorrect clinical diagnosis without laboratory confirmation may lead to years of unneeded antiviral therapy. Finally, in women who may become pregnant, a diagnosis of genital herpes has serious implications.

Type-specific serologic tests use HSV glycoprotein G antigens with low cross-reactivity to distinguish between HSV-1 and HSV-2 infections. Older serologic assays, which use highly cross-reactive whole-virus antigens, should not be used. HSV IgG can be detected by means of a type-specific ELISA beginning approximately 3 weeks after initial infection. With the use of Western blotting as the reference assay, the sensitivity of these assays for HSV-2 is 80 to 98%, and the specificity is 93 to 97%; the sensitivity of these assays for HSV-1 is lower at 69 to 98%, and the specificity is 92 to 95%.[18-21] Although type-specific ELISAs are very useful, they can yield false positive results, particularly when they are used in populations with a low prevalence of infection and when they are interpreted at low index values. Such results may require confirmatory testing with a different assay (e.g., a rapid point-of-care test or Western blotting).[22]

Detection of HSV-2-specific IgG is indicative of genital herpes, even in patients who do not have a clinical history of the infection. The presence of HSV-1–specific IgG is consistent with either genital or nongenital (e.g., orolabial) infection. Serologic testing is particularly useful when a patient has a history that suggests recurrent genital symptoms but does not have an active lesion that is suitable for virologic testing. If one person in a couple is known to have genital herpes, serologic testing can inform counseling regarding risks of transmission.

Viral culture was once the accepted reference test, but it is slow and relatively insensitive in patients with lesions that have progressed beyond the ulcerative stage. In many clinical laboratories, Food and Drug Administration–approved

Table 1. Antiviral Therapy for Genital Herpes.*

Indication and Agent	Oral Doses†
Initial therapy for genital herpes	
Acyclovir	400 mg 3 times a day for 7–10 days or 200 mg 5 times a day for 7–10 days
Valacyclovir	1 g twice a day for 7–10 days
Famciclovir	250 mg 3 times a day for 7–10 days
Episodic therapy for recurrent genital herpes	
Acyclovir	400 mg 3 times a day for 5 days or 800 mg twice a day for 5 days or 800 mg 3 times a day for 2 days
Valacyclovir	500 mg twice a day for 3 days or 1 g once a day for 5 days
Famciclovir	125 mg twice a day for 5 days or 1 g every 12 hr for 2 doses or 500 mg for 1 dose followed by 250 mg twice a day for 2 days
Suppressive therapy	
For recurrent genital herpes	
Acyclovir	400 mg twice a day
Valacyclovir	500 mg once a day or 1 g once a day
Famciclovir	250 mg twice a day
In pregnancy (beginning at 36 wk of gestation)‡	
Acyclovir	400 mg 3 times a day
Valacyclovir	500 mg twice a day

* Data are from Workowski and Bolan.[22]
† Dose adjustment may be required in patients with substantial renal dysfunction. See the manufacturers' package inserts.
‡ Acyclovir and valacyclovir are both Food and Drug Administration (FDA) Pregnancy Category B drugs (animal reproduction studies have not shown a risk to the fetus, and adequate and well-controlled studies in pregnant women are lacking) and are not FDA-approved for use in pregnancy.

nucleic acid amplification assays such as PCR have replaced viral culture. PCR assay of a lesion is rapid, type-specific, and cost-competitive.[23] The sensitivity of PCR assays depends on the lesion stage and approaches 100% when the assays are used for vesicles or wet ulcers; yields for dry ulcers or crusts are lower but are still superior to those of culture. Viral antigen detection assays are available but are less sensitive than PCR assays and do not allow viral typing.

ANTIVIRAL THERAPY

Acyclovir, valacyclovir, and famciclovir are effective therapies for genital herpes caused by HSV-1 or HSV-2 (although most published efficacy data relate to HSV-2). These antiviral medications have excellent safety profiles and rarely cause drug–drug interactions or allergic reactions. Since the efficacy is generally similar, selection of a specific drug is based on the convenience of administration, cost, and clinician preference. Intravenous acyclovir should be used when the manifestations of genital herpes are especially severe or are accompanied by complications, particularly in immunocompromised patients. Topical antiviral therapy for genital herpes is less effective than systemic therapy and is not recommended.

Initial (and especially primary) genital HSV infection is associated with more severe and prolonged manifestations than occur with recurrent genital herpes, and warrants treatment. Randomized, controlled trials have shown that antiviral therapy reduces the times to symptom alleviation, lesion healing, and termination of viral shedding by approximately 2, 4, and 7 days, respectively.[24,25] The benefit is maximized if antiviral therapy is initiated within 72 hours after the onset of lesions. The most convenient regimen is valacyclovir at a dose of 1 g orally twice daily for 7 to 10 days (Table 1).[22] Analgesics and warm sitz baths provide symptom relief.

Patients with symptomatic recurrences of genital herpes can receive episodic therapy (1 to 5 days of therapy for an acute recurrence) or suppressive therapy (long-term daily drug administration to reduce the frequency of symptomatic recurrences). Both episodic and suppressive therapies result in clinically significant improvements in perceived quality of life.[26] Randomized trials indicate that antiviral treatment initiated within 24 hours after the onset of symptoms reduces the times to symptom alleviation, lesion healing, and viral shedding by 1 to 2 days.[27-29] Acyclovir, valacyclovir, and famciclovir have similar efficacy for symptomatic recurrences. The most convenient regimen is famciclovir at a dose of 1 g administered orally every 12 hours for 2 doses (Table 1).[22]

Randomized trials showed that the proportion of patients with a symptomatic recurrence over the course of 4 months was significantly lower among those who received daily suppressive therapy than among those who received placebo (approximately 25 to 30% vs. 80 to 85%).[26,30-32] Many patients have no further outbreaks after they begin to receive suppressive therapy.

Suppressive therapy also significantly reduces

the frequency of asymptomatic shedding of HSV-2. In a 7-week study comparing valacyclovir with placebo, asymptomatic viral shedding was detected by PCR on 27.1% of the days in patients who received placebo and on 6.1% of the days in patients who received valacyclovir (relative risk with valacyclovir, 0.18; 95% confidence interval [CI], 0.12 to 0.26; P<0.001).[33] This reduction in frequency of shedding reduces the risk of transmission to an HSV-2–negative partner.[13,33]

In a study involving immunocompetent HSV-2–discordant heterosexual couples, the probability that a partner would acquire genital HSV-2 infection was significantly lower among those who received suppressive therapy with valacyclovir (at a dose of 500 mg once daily for 8 months) than among those who received placebo (14 of 743 susceptible partners with valacyclovir [1.9%] vs. 27 of 741 susceptible partners with placebo [3.6%]; hazard ratio, 0.25; 95% CI, 0.08 to 0.75; P=0.008).[13] The option of suppressive therapy should be discussed with all patients who have genital herpes, even those who have relatively infrequent symptomatic recurrences.

All three drugs provide benefit as suppressive therapy, although one study showed that valacyclovir was superior to famciclovir.[32] The most convenient regimen is valacyclovir at a dose of 500 or 1000 mg orally once daily (Table 1).[22] If the rate of symptomatic recurrence with the use of once-daily therapy remains unacceptably high to the patient, a higher dose or twice-daily administration can be tried. Long-term suppressive therapy is almost never associated with the development of acyclovir-resistant virus in immunocompetent patients.

PSYCHOLOGICAL EFFECTS

Patients who have received a new diagnosis of genital herpes should be informed that this disease is manageable and that it need not have a major effect on their sexuality. If a patient is in a long-term relationship, it may be helpful to have his or her partner participate in the discussion. Despite reassurances, responses such as anger, shame, depression, fear of rejection by sexual partners, and fear of discovery are common. In most cases, however, these reactions are short-lived and do not result in lasting psychological difficulties.[34]

REDUCING THE RISK OF SEXUAL TRANSMISSION

In addition to antiviral suppression, other strategies can reduce the rates of transmission of HSV. Patients should be encouraged to disclose their history of genital herpes to their sex partners, since this disclosure is associated with a reduced risk of transmission (although it is unclear exactly how disclosure reduces risk).[35] Since high titers of HSV are shed from symptomatic genital lesions, patients should remain abstinent until lesions have healed. Patients with minimally symptomatic recurrent HSV-2 genital herpes can become attuned to the subtle manifestations of recurrences (e.g., minor irritation and itching) and should avoid sexual activity until the episode resolves.

The use of condoms, which reduces the risk of transmission of HSV from an infected partner to a susceptible partner by approximately 30%, should be routinely recommended.[36,37] Condoms are more effective in preventing HSV transmission from men to women than from women to men.[38] The efficacy of administration of antiviral therapy as prophylaxis for an uninfected partner or as postexposure prophylaxis against HSV has not been adequately studied.

REDUCING THE RISK OF VERTICAL TRANSMISSION

Prevention of neonatal herpes hinges on prevention of maternal acquisition of genital herpes during late pregnancy and prevention of neonatal exposure to HSV during delivery. Routine serologic screening of all pregnant women to detect HSV is not cost-effective and is not currently recommended. During the third trimester, pregnant women who do not have a history of genital herpes should abstain from sexual contact with partners who are known to have herpes. Serologic testing of sexual partners of HSV-susceptible pregnant women is appropriate, since the use of safe-sex practices is increased if these women are informed of a partner's positive HSV serologic status.[39] The efficacy of suppressive antiviral therapy administered to HSV-2-infected men to prevent transmission to their susceptible pregnant partners is not known.

At the onset of labor, all pregnant women should be questioned about symptoms of genital herpes and examined for herpetic lesions. If lesions are discovered, cesarean delivery should be undertaken to reduce the risk of neonatal herpes. In a prospective cohort study, cesarean deliv-

ery was associated with a significantly lower risk of HSV transmission to the neonate than vaginal delivery among women who had active shedding of HSV at the onset of labor (1.2% vs. 7.7%).[17]

Many obstetricians recommend suppressive therapy with acyclovir or valacyclovir beginning at 36 weeks of gestation in women who have a history of symptomatic genital herpes.[40] Both agents appear to be safe, although they are not licensed for use in pregnancy.[41] Antiviral suppression reduces the frequency of recurrences of genital herpes in late pregnancy and thus reduces the necessity for cesarean delivery.[42] Although this approach is presumed to reduce the risk of neonatal herpes, studies have not been adequately powered to reliably assess that outcome.

AREAS OF UNCERTAINTY

Candidate vaccines against HSV have been studied in large-scale clinical trials, but only marginal protection has been seen in subgroup populations.[43] The development of preventive and therapeutic vaccines against HSV is an area of active research.[44]

Routine serologic screening for HSV is not currently recommended. However, this subject remains a topic for debate.[45-47]

GUIDELINES

Guidelines for the treatment of genital herpes have been published by the Centers for Disease Control and Prevention[22] and by European experts in sexually transmitted diseases.[48] U.S. and Canadian obstetrical societies have published guidelines for the management of genital herpes in pregnant women.[40,49,50] The recommendations in this article are consistent with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The woman in the vignette probably has genital herpes, as indicated by her history and positive HSV-2 serologic status. The duration and source of her HSV-2 infection cannot be determined, although her seronegative husband can be excluded as the source. She has noticed symptoms only within the past year; however, she could have been infected at any time since she became sexually active, since initial infection may be subclinical.

The frequency of recurrence of genital herpes is more consistent with HSV-2 than with HSV-1, but both are potential pathogens in this patient. Distinguishing between them would require further testing with the use of PCR or culture of lesions during an outbreak. The patient should receive counseling regarding the natural history of genital herpes, the risks of transmission, and the treatment options. All patients with a diagnosis of genital herpes should be offered comprehensive screening for other sexually transmitted diseases, including HIV.

To minimize the risk of transmission to her HSV-2–seronegative husband, this patient should be offered daily suppressive antiviral therapy. This therapy reduces the frequency of HSV-2 reactivation (symptomatic and asymptomatic) and reduces the risk of transmission by almost 50%. Her husband should use condoms, which will provide additional protection. The couple should avoid sexual contact while she has a symptomatic lesion. They should be informed that risk reduction provided by these interventions is not absolute, and transmission could still occur. If they decide to attempt conception, the patient should discuss her history of genital herpes with her obstetrician at the prenatal visit.

Dr. Gnann reports receiving fees for serving on data and safety monitoring boards from Watermark Research Partners (a contract research organization paid by GlaxoSmithKline) and BioCryst, and fees for serving on a clinical adjudication committee from Merck; and Dr. Whitley, serving on advisory boards and receiving compensation, travel support, and stock options for his role on the board of directors from Gilead Sciences and receiving fees for serving on data and safety monitoring committees from GlaxoSmithKline and Merck. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Bradley H, Markowitz LE, Gibson T, McQuillan GM. Seroprevalence of herpes simplex virus types 1 and 2 — United States, 1999-2010. J Infect Dis 2014;209:325-33.
2. Fanfair RN, Zaidi A, Taylor LD, Xu F, Gottlieb S, Markowitz L. Trends in seroprevalence of herpes simplex virus type 2 among non-Hispanic blacks and non-Hispanic whites aged 14 to 49 years — United States, 1988 to 2010. Sex Transm Dis 2013;40:860-4.
3. Stanberry LR, Rosenthal SL, Mills L, et al. Longitudinal risk of herpes simplex virus (HSV) type 1, HSV type 2, and cytomegalovirus infections among young adolescent girls. Clin Infect Dis 2004;39:1433-8.

4. Okafor N, Rosenberg ES, Luisi N, et al. Disparities in herpes simplex virus type 2 infection between black and white men who have sex with men in Atlanta, GA. Int J STD AIDS 2015;26:740-5.
5. Abu-Raddad LJ, Magaret AS, Celum C, et al. Genital herpes has played a more important role than any other sexually transmitted infection in driving HIV prevalence in Africa. PLoS ONE 2008;3(5): e2230.
6. Xu F, Lee FK, Morrow RA, et al. Seroprevalence of herpes simplex virus type 1 in children in the United States. J Pediatr 2007;151:374-7.
7. Ryder N, Jin F, McNulty AM, Grulich AE, Donovan B. Increasing role of herpes simplex virus type 1 in first-episode anogenital herpes in heterosexual women and younger men who have sex with men, 1992-2006. Sex Transm Infect 2009;85: 416-9.
8. Bernstein DI, Bellamy AR, Hook EW III, et al. Epidemiology, clinical presentation, and antibody response to primary infection with herpes simplex virus type 1 and type 2 in young women. Clin Infect Dis 2013;56:344-51.
9. Engelberg R, Carrell D, Krantz E, Corey L, Wald A. Natural history of genital herpes simplex virus type 1 infection. Sex Transm Dis 2003;30:174-7.
10. Leone P, Fleming DT, Gilsenan AW, Li L, Justus S. Seroprevalence of herpes simplex virus-2 in suburban primary care offices in the United States. Sex Transm Dis 2004;31:311-6.
11. Schulte JM, Bellamy AR, Hook EW III, et al. HSV-1 and HSV-2 seroprevalence in the United States among asymptomatic women unaware of any herpes simplex virus infection (Herpevac Trial for Women). South Med J 2014;107:79-84.
12. Tronstein E, Johnston C, Huang ML, et al. Genital shedding of herpes simplex virus among symptomatic and asymptomatic persons with HSV-2 infection. JAMA 2011;305:1441-9.
13. Corey L, Wald A, Patel R, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. N Engl J Med 2004;350:11-20.
14. Dhankani V, Kutz JN, Schiffer JT. Herpes simplex virus-2 genital tract shedding is not predictable over months or years in infected persons. PLoS Comput Biol 2014; 10(11):e1003922.
15. Schiffer JT, Mayer BT, Fong Y, Swan DA, Wald A. Herpes simplex virus-2 transmission probability estimates based on quantity of viral shedding. J R Soc Interface 2014;11:20140160.
16. James SH, Kimberlin DW. Neonatal herpes simplex virus infection: epidemiology and treatment. Clin Perinatol 2015; 42:47-59, viii.
17. Brown ZA, Wald A, Morrow RA, Selke S, Zeh J, Corey L. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. JAMA 2003;289:203-9.
18. Ashley-Morrow R, Nollkamper J, Robinson NJ, Bishop N, Smith J. Performance of focus ELISA tests for herpes simplex virus type 1 (HSV-1) and HSV-2 antibodies among women in ten diverse geographical locations. Clin Microbiol Infect 2004; 10:530-6.
19. Mark HD, Nanda JP, Roberts J, Rompalo A, Melendez JH, Zenilman J. Performance of focus ELISA tests for HSV-1 and HSV-2 antibodies among university students with no history of genital herpes. Sex Transm Dis 2007;34:681-5.
20. Morrow RA, Friedrich D, Krantz E. Performance of the Focus and Kalon enzyme-linked immunosorbent assays for antibodies to herpes simplex virus type 2 glycoprotein G in culture-documented cases of genital herpes. J Clin Microbiol 2003;41:5212-4.
21. Summerton J, Riedesel M, Laeyendecker O, et al. Effect of sexually transmitted disease (STD) coinfections on performance of three commercially available immunosorbent assays used for detection of herpes simplex virus type 2-specific antibody in men attending Baltimore, Maryland, STD clinics. Clin Vaccine Immunol 2007;14:1545-9.
22. Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep 2015; 64(RR-03):1-137.
23. Ramaswamy M, McDonald C, Smith M, et al. Diagnosis of genital herpes by real time PCR in routine clinical practice. Sex Transm Infect 2004;80:406-10.
24. Bryson YJ, Dillon M, Lovett M, et al. Treatment of first episodes of genital herpes simplex virus infection with oral acyclovir — a randomized double-blind controlled trial in normal subjects. N Engl J Med 1983;308:916-21.
25. Fife KH, Barbarash RA, Rudolph T, Degregorio B, Roth R. Valaciclovir versus acyclovir in the treatment of first-episode genital herpes infection: results of an international, multicenter, double-blind, randomized clinical trial. Sex Transm Dis 1997;24:481-6.
26. Fife KH, Almekinder J, Ofner S. A comparison of one year of episodic or suppressive treatment of recurrent genital herpes with valacyclovir. Sex Transm Dis 2007;34:297-301.
27. Reichman RC, Badger GJ, Mertz GJ, et al. Treatment of recurrent genital herpes simplex infections with oral acyclovir: a controlled trial. JAMA 1984;251:2103-7.
28. Sacks SL, Aoki FY, Diaz-Mitoma F, Sellors J, Shafran SD. Patient-initiated, twice-daily oral famciclovir for early recurrent genital herpes: a randomized, double-blind multicenter trial. JAMA 1996;276:44-9.
29. Tyring SK, Douglas JM Jr, Corey L, Spruance SL, Esmann J. A randomized, placebo-controlled comparison of oral valacyclovir and acyclovir in immunocompetent patients with recurrent genital herpes infections. Arch Dermatol 1998; 134:185-91.
30. Diaz-Mitoma F, Sibbald RG, Shafran SD, Boon R, Saltzman RL. Oral famciclovir for the suppression of recurrent genital herpes: a randomized controlled trial. JAMA 1998;280:887-92.
31. Douglas JM, Critchlow C, Benedetti J, et al. A double-blind study of oral acyclovir for suppression of recurrences of genital herpes simplex virus infection. N Engl J Med 1984;310:1551-6.
32. Wald A, Selke S, Warren T, et al. Comparative efficacy of famciclovir and valacyclovir for suppression of recurrent genital herpes and viral shedding. Sex Transm Dis 2006;33:529-33.
33. Gupta R, Wald A, Krantz E, et al. Valacyclovir and acyclovir for suppression of shedding of herpes simplex virus in the genital tract. J Infect Dis 2004;190:1374-81.
34. Ross K, Johnston C, Wald A. Herpes simplex virus type 2 serological testing and psychosocial harm: a systematic review. Sex Transm Infect 2011;87:594-600.
35. Wald A, Krantz E, Selke S, Lairson E, Morrow RA, Zeh J. Knowledge of partners' genital herpes protects against herpes simplex virus type 2 acquisition. J Infect Dis 2006;194:42-52.
36. Wald A, Langenberg AG, Krantz E, et al. The relationship between condom use and herpes simplex virus acquisition. Ann Intern Med 2005;143:707-13.
37. Martin ET, Krantz E, Gottlieb SL, et al. A pooled analysis of the effect of condoms in preventing HSV-2 acquisition. Arch Intern Med 2009;169:1233-40.
38. Magaret AS, Mujugira A, Hughes JP, et al. Effect of condom use on per-act HSV-2 transmission risk in HIV-1, HSV-2-discordant couples. Clin Infect Dis 2016;62: 456-61.
39. Delaney S, Gardella C, Daruthayan C, et al. A prospective cohort study of partner testing for herpes simplex virus and sexual behavior during pregnancy. J Infect Dis 2012;206:486-94.
40. ACOG Committee on Practice Bulletins. ACOG practice bulletin: clinical management guidelines for obstetrician-gynecologists. No. 82, June 2007. Management of herpes in pregnancy. Obstet Gynecol 2007;109:1489-98.
41. Stone KM, Reiff-Eldridge R, White AD, et al. Pregnancy outcomes following systemic prenatal acyclovir exposure: conclusions from the international Acyclovir Pregnancy Registry, 1984-1999. Birth Defects Res A Clin Mol Teratol 2004;70:201-7.
42. Sheffield JS, Hill JB, Hollier LM, et al. Valacyclovir prophylaxis to prevent recurrent herpes at delivery: a randomized clinical trial. Obstet Gynecol 2006;108: 141-7.

43. Belshe RB, Leone PA, Bernstein DI, et al. Efficacy results of a trial of a herpes simplex vaccine. N Engl J Med 2012;366:34-43.
44. Johnston C, Koelle DM, Wald A. Current status and prospects for development of an HSV vaccine. Vaccine 2014;32:1553-60.
45. Geretti AM. Genital herpes. Sex Transm Infect 2006;82:Suppl 4:iv31-4.
46. Mark HD. Asymptomatic sexually active adolescents and young adults should not be screened for herpes simplex virus. JAMA Pediatr 2013;167:691-2.
47. Wald A. Knowledge is power: a case for wider herpes simplex virus serologic testing. JAMA Pediatr 2013;167:689-90.
48. Patel R, Alderson S, Geretti A, et al. European guideline for the management of genital herpes, 2010. Int J STD AIDS 2011;22:1-10.
49. Money D, Steben M. SOGC clinical practice guidelines: guidelines for the management of herpes simplex virus in pregnancy. Number 208, June 2008. Int J Gynaecol Obstet 2009;104:167-71.
50. Money D, Steben M. SOGC clinical practice guidelines: genital herpes: gynaecological aspects. Number 207, April 2008. Int J Gynaecol Obstet 2009;104:162-6.