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GENITAL HERPES

Common questions about diagnosis and transmission

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Educational Objectives

At the conclusion of this activity, participants should be able to:

- Discuss current approaches to testing for herpesvirus (HSV) infection to improve the diagnosis of genital herpes (GH) and to reduce the risk of transmission
- Encourage the counseling of HSV-infected patients and their partners by providing a better understanding of the natural history of GH and viral shedding to reduce the risk of transmission of HSV

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Renewed interest in genital herpes (GH) began in 1981 with the commercial introduction of acyclovir, the first oral antiviral medication.[1,2] This breakthrough was followed by a number of key developments, including:

- Recognition that women outnumber men with herpesvirus-2 (HSV-2) infection 2 to 1[3]
- Approval of 2 new, longer-acting antiviral agents, valacyclovir and famciclovir
- Greatly improved testing in the form of amplified DNA swab tests and type-specific serologic (antibody) tests
- The emergence of herpesvirus-1 (HSV-1) as a major cause of genital herpes
- Advances in understanding the natural history of infection and disease including antiviral shedding, HSV/HIV interactions, and the successful use of antivirals to help prevent further transmission of infection[4-7]

The following commonly asked questions focus on clinical presentation, diagnosis, asymptomatic viral shedding, and transmission of infection in nonpregnant women and their sexual partners.

Q: How common is GH and what are its clinical characteristics?

A: GH is a very common viral infection. Approximately 50 million people in the United States are infected with HSV-2, and an estimated 10 to 15 million have genital HSV-1.[3,8,9] Following initial infection, these viruses become nerve-based in the trigeminal ganglion in the face (HSV-1) and sacral ganglia in the lower back

What is the difference between genital herpes caused by HSV-2 and by HSV-1?

HSV-2 GH is caused by viral transmission following penile-vaginal and penile-anal intercourse.[1] Of the 50 million infected individuals, 15% to 20% (8 to 10 million people in the United States) have the easily recognizable, classic clinical presentations. The remaining 40 million people with HSV-2 appear to have recurrent lower genital-tract inflammation that, because of the absence of ulcerative GH lesions, is rarely associated with GH by either the patient or clinician. The majority of these 40 million individuals have recurrent lower genital tract inflammation without ulcerative lesions. Patients with so called "atypical GH" can present with itching, redness, mild to moderate pain, discharge, rash, and dysuria.[2,3] In response to these symptoms, patients often use a variety of over-the-counter nonprescription remedies including antihemorrhoidals, antibacterial and antifungal creams, ointments and sprays, and topical corticosteroids.

HSV-1 GH is often much less inflammatory in its clinical presentation than is HSV-2. It is usually caused by transmission of HSV-1 from the lips to the genitals during oral sex.[4] Initial HSV-1 GH outbreaks are shorter than those caused by HSV-2 (1 to 3 days vs 1 to 2 weeks), less recurrent in the first few years (annual outbreaks vs every 2 to 4 months), and less likely to be associated with asymptomatic viral shedding (AVS).[5-7] Many clinical cases may be undiagnosed due to a short first outbreak period and infrequent clinical recurrences. Acquisition of HSV-1 GH through penile-vaginal or penile-anal intercourse is less likely than through oral sex due to infrequent outbreaks and limited viral shedding in the genital area associated with HSV-1 infection of the sacral ganglia. It is difficult to accurately estimate the number of individuals with sexually acquired HSV-1 GH since about two-thirds of Americans are infected with orolabial HSV-1 during early childhood.

Approximately half of those infected with HSV-1 will go on to develop cold sores or fever blisters, usually beginning in the peripubertal period. This extensive level of pre-sexually acquired HSV-1 infection may help explain the milder clinical course and less frequent rate of viral reactivation of HSV-1 GH compared to HSV-2 GH.

Also, increased and earlier oral-genital sexual activity among adolescents and young adults are thought to account for increasing rates of HSV-1 GH infection. Although HSV-2 GH infection is responsible for at least 95% of recurrent GH clinical outbreaks, GH due to HSV-1 infection accounts for an increasing proportion of first clinical GH episodes reaching 50% or more in some groups such as university students.[8-10]

References

1. Corey L, Adams HG, Brown ZA, et al. Genital herpes simplex virus infections: clinical manifestations, course, and complications. Ann Intern Med. 1983;98:958-972.
2. Ashley RL, Wald A. Genital herpes: review of the epidemic and potential use of type-specific serology. Clin Microbiol Rev. 1999;12:1-8.
3. Department of Health and Human Services, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2006. MMWR. 2006;55:1-94.
4. Lafferty WE, Downey L, Celum C, et al. Herpes simplex virus type 1 as a cause of genital herpes: impact on surveillance and prevention. J Infect Dis. 2000;181:1454-1457.
5. Benedetti J, Corey L, Ashley R. Recurrence rates in genital herpes after symptomatic first-episode infection. Ann Intern Med. 1994;121:847-854.
6. Wald A, Zeh J, Selke S, et al. Virologic characteristics of subclinical and symptomatic genital herpes infections. N Engl J Med. 1995:333:770-775.
7. Langenberg AG, Corey L, Ashley RL, et al, for the Chiron HSV Vaccine Study Group. A prospective study of new infections with herpes simplex virus type 1 and type 2. N Engl J Med. 1999:341:1432-1438.
8. Roberts CM, Pfister JR, Spear SJ. Increasing proportion of herpes simplex virus type 1 as a cause of genital herpes infection in college students. Sex Transm Dis. 2003;30:797-800.
9. Roberts CM. Genital herpes in young adults: changing sexual behaviours, epidemiology and management. Herpes. 2005;12:10-14.
10. Xu F, Sternberg MR, Kottiri BJ, et al. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. JAMA. 2006;296:964-973.

(HSV-2 and HSV-1). In these nerve-based locations, herpesviruses are apparently protected from full clearance by the immune system, hence their designation as lifelong infections.

Clinical characteristics of GH include recurrent symptoms in the genital area, such as itching, burning, and pain accompanied first by erythema and then classic inflammatory vesicular lesions that ultimately progress to ulcers and crusting, finally healing to normal-appearing skin.

Q: Which patients are at greatest risk of acquiring GH?

A: Approximately 1 in 4 women is infected with GH—about twice as many as men.[9,10] The greater susceptibility of women to GH compared to men may reflect anatomic, immunologic, and unexplained differences. Unlike bacterial sexually transmitted diseases (STD), in which socioeconomic characteristics significantly impact infection rates, in the United States, married people, college graduates,

and higher-income (more than $100,000) adults have rates similar to the overall rate of GH infection. Significant racial disparities in prevalence exist, especially for African Americans and, to a lesser degree, Hispanic Americans, for reasons that have remained largely unexplained.[9]

Differences in sexual and preventative behaviors (eg, number of sex partners, use of condoms) that may explain the risk of acquiring bacterial STDs, such as chlamydia or gonorrhea, do not predict who will become infected with HSV-2. With one-quarter or more of prospective sexual partners infected with HSV-2, the risk of acquiring HSV-2 is less dependent on the number of sex partners than on whether sex partners have been infected. The common belief that patients who acquire GH have a substantially larger number of sex partners than those who are not infected is incorrect, when considering the vast majority of those infected with GH.[11]

In the typical primary care and women's health practice, about 3% to 4% of patients have a history of GH, which largely reflects those with classic GH signs and symptoms. This contrasts with the 25% or more who are actually infected with genital HSV-2, most with unrecognized atypical or asymptomatic GH. This difference in percentages contributes to the misconception that GH is rarely seen in primary care.

Diagnosing genital herpes

Q: Why do so many GH infections remain undiagnosed?

A: For decades, clinicians have used the appearance of vesiculoulcerative lesions and associated symptoms to make a diagnosis of GH. This syndromic approach is highly problematic for a number of reasons. Even in the hands of experienced clinicians, more than 1 in 5 patients presenting with classic GH signs and symptoms do not actually have GH. In addition, patients with a history of genital irritation may not have lesions or symptoms at the time of their office visit. Some may not have classical stigmata, instead presenting with nonspecific symptoms such as genital itching, burning, dysuria, discharge, and atypical lesions such as rashes or fissures. Patients with GH often will report what they think they have as other conditions including urinary tract infection, vaginitis, yeast infection, vulvitis, perineal and perianal irritation, condom and spermicidal allergies, and postcoital soreness.[12,13]

Failure by the CDC and other guideline-setting groups to agree which STD tests should be included in a standard STD screening panel and to make recommendations for routine inclusion of HSV-2 serologic testing when performing STD evaluation further contribute to underdiagnosis of GH.[12]

TABLE Clinical scenarios for serologic testing and screening for genital herpes

- To confirm a visual diagnosis, especially with a negative GH culture or no culture performed
- When patients have recurrent lower genital-tract clinical symptoms suggesting GH but not classic GH lesions
- In the absence of GH lesions
- To determine whether the current or previous sex partners of a patient with GH also have GH
- As part of STD screening and when a patient has another STD, reflecting the increased risk of also having GH
- When a patient requests his or her GH infection status

GH, genital herpes; STD, sexually transmitted disease.

Sources: Department of Health and Human Services, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2006.MMWR. 2006;55:1-94. ACOG Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 46. Gynecological Herpes Simplex Virus Infections. Obstet Gynecol. 2004;104:1111-1117.

Q: Why is it important to know which herpesvirus (HSV-2 or HSV-1) is responsible for the patient's GH?

A: GH caused by HSV-2 infection generally has more serious clinical consequences than HSV-1, with much higher rates of viral shedding, longer and more frequent recurrences, and greater likelihood of genital-to-genital transmission. HSV-2 is more likely to present as an atypical outbreak than HSV-1; it is often associated with reactivation during and particularly at the end of pregnancy as well as with neonatal infection. In addition, compared to patients with HSV-1, patients with HSV-2 infection are much more likely to receive daily antiviral therapy to reduce the frequency of clinical outbreaks and to prevent transmission to uninfected partners.

Q: Why should swab tests be used and how accurate are they?

A. HSV cultures are inexpensive but the yield can be low, often less than 50%, especially if the specimen is not obtained during the first few days after the outbreak begins. In addition to low sensitivity (high rates of false negatives), cultures can suffer from transport problems and prolonged result-reporting times, sometimes in excess of a week.[14] Some laboratories fail to report positive culture results by type, either HSV-1 or HSV-2, which delays a type-specific diagnosis and requires a second specimen.

Amplified DNA swab tests, often referred to as PCR (polymerase chain reaction) assays, are able to identify smaller amounts of viruses later in the course of the outbreak and are less dependent on careful sampling and transport. In addition, results can be available in a day or two.[15,16] Although clearly superior to culture in diagnosing GH, PCR assays are usually far more expensive and also may not be reimbursed by some third-party payers when used in outpatient care. PCR assays are not approved by the US Food and Drug Administration (FDA) for genital specimens, but because of better sensitivity, they are recommended for this use by most viral disease experts.[17]

Q: How should serologic tests be used and interpreted?

A. The 2006 US Centers for Disease Control (CDC) STD Treatment Guidelines expand on previous recommendations regarding the key role type-specific serologic (antibody) tests play in diagnosis of HSV infection.[12] These tests accurately distinguish HSV-2 antibodies from those of HSV-1 without cross-reactivity problems.[18]

Newer HSV glycoprotein G–based, type-specific serologic tests can be sent to medical laboratories or performed at the point-of-care. The most commonly used antibody tests for GH are the HerpeSelect-2 and HerpeSelect-1 for HSV-2, and HSV-1 IgG (immunoglobin G) long-term antibodies, respectively.

A positive HSV-2 antibody test means that the patient has genital herpes. In general, a positive HSV-1 antibody test usually means that the patient has orolabial herpes, since about two-thirds of the population have HSV-1 trigeminal nerve infection by adolescence, whereas a much smaller percent are HSV-1 positive due to HSV-1 GH.

In terms of test interpretation, the window period for the HerpeSelect-1 and HerpeSelect-2 tests is approximately 3 weeks for the earliest appearance of antibodies after infection and 16 weeks for the point by which the vast majority of those infected have acquired IgG antibodies.[19,20]

For point-of-care testing, the new, more accurate, and easier-to-perform HerpeSelect Direct, as well as the older Biokit HSV-2 Rapid Test and SureVue HSV-2 kit, can be used to detect HSV-2 antibodies from capillary blood or serum during an office visit.[21]

While some clinicians order IgM (immunoglobulin M) antibody tests to differentiate initial from recurrent GH infection, IgM antibody tests are not type-specific, are unreliable, and should not be used in making a GH diagnosis.[20] Patients with reported positive IgM antibodies for HSV-1 and HSV-2 in the presence of persistently negative IgG serologic tests for HSV-2 and HSV-1 are very unlikely to have genital herpes.

Call for mainstream testing

The CDC recently issued recommendations to mainstream the use of HIV tests, with the goal of reaching those who have HIV but are unaware of it. A similar approach is warranted for HSV-2 infection. It is far better for patients to have an antibody test and learn their HSV-2 status prior to infecting a sex partner. Such knowledge provides patients with the opportunity to practice prevention and to inform sex partners of their HSV-2 infection status prior to sexual intercourse.[22] Studies show that the latter behavior is associated with reduced transmission. In addition, adverse psychosocial consequences are more likely to occur among patients who inadvertently discover they have GH by infecting a sex partner who then develops clinical GH.[23,24]

Q: Is there a simple algorithm for the use of swab and serologic tests in diagnosing patients with suspected GH lesions?

A: Swab tests (herpes culture or PCR assay) should always be performed when suspected classic or atypical GH lesions are present. A negative swab test does not rule out that genital lesions are caused by HSV-2 or HSV-1.[14]

There are 2 approaches to using antibody testing to evaluate patients with suspected GH lesions. Clinicians first perform a swab test, and if the test is negative, they perform another antibody test the following week.

The alternative is to perform HSV-2 antibody testing at the same time as the swab test. Many clinicians prefer this approach because the swab test is often negative even in the presence of herpesviruses, and delaying an HSV antibody test may delay the diagnosis of GH. Also, more than half of patients with a first GH outbreak already have GH antibodies. This is because their initial GH infection was asymptomatic or unrecognized, and their first lesional outbreak does not represent true primary infection but, rather, the first clinical outbreak of a previously acquired GH infection.[10,13,25,26]

In terms of whether to test for HSV-2 antibodies only or both HSV-1 and HSV-2 antibodies, the former approach often makes more sense. A positive HSV-1 antibody test usually reflects orolabial infection acquired in early childhood rather than GH due to HSV-1. If the initial HSV-2 antibody test is negative, it should be repeated 3 months later. A positive HSV-2 antibody test at 3 months following an initial negative HSV-2 test reflects true primary infection. A persistently negative HSV-2 test at 3 months suggests that the original suspected GH lesion was most likely due to HSV-1.

Alternatively, if both HSV-1 and HSV-2 antibody tests are performed, and the HSV-1 antibody test is initially negative, and then 3 months after retesting is positive, this reflects true primary GH infection due to HSV-1. If the initial HSV-1 antibody test is positive and initial and follow-up HSV-2 tests are negative, this reflects an HSV-1 infection at either an orolabial or genital site, and a GH diagnosis cannot be made. In cases where the diagnosis or site of GH infection is indeterminate, re-swabbing subsequent lesions may be of value in making a definitive diagnosis.

Q: How often does asymptomatic viral shedding occur?

A: Asymptomatic viral shedding (AVS) occurs frequently and is responsible for up to 70% of GH transmission to uninfected sex partners.[27] AVS is not only common and occurs frequently in almost all patients, it occurs even in those with longstanding, recognized GH and clinically silent infection.[12] The presence of herpesviruses in the genital area in the absence of lesions is a challenging concept for many patients.

Although asymptomatic AVS was previously thought to occur only at the principal clinical outbreak location or locations during non-outbreak periods, it is now known that AVS can occur in multiple locations in the lower genital tract (cervix, vagina, vulva, penis, scrotum, perineum, urethra, and perianal region), either simultaneously with clinical outbreaks or independent of them. As a result, patients cannot predict if, when, or where they may have asymptomatic viral shedding.[28]

Using PCR assays, viral shedding studies have established AVS rates of 3% to 27% of days, the equivalent of 1 to 8 days per month.[28] AVS is unpredictable, with more than half of AVS episodes occurring more than a week before or after clinical outbreaks.

Q: What are the key correlates of asymptomatic viral shedding and what role do these correlates play in the transmission of GH?

A. Studies over the past 15 years have substantially increased knowledge about AVS. It is most frequent during the first 12 months after acquiring HSV-2, and in patients with a newly acquired infection, the proportion of days with AVS is twice as great as in patients with an established history of GH (32% vs 14%).[12]

It was previously assumed that AVS was more common among patients with greater numbers of clinical outbreaks. However, studies have demonstrated no significant difference among women with 1 to 12 outbreaks a year, as compared to women with no outbreaks.[28,29]

Although the frequency of clinical outbreaks falls steadily over the first decade after GH diagnosis, AVS patterns are different. The percentage of days with AVS are highest in the first year after GH

diagnosis, followed by a plateau at approximately one-third to one-half of the first year's AVS rate. These rates continue at that level for well over a decade.[30] AVS rates are significantly affected by the use of daily antiviral therapy.

Daily medication reduces asymptomatic and symptomatic viral shedding rates by 70% to 80%.[5,31] This explains the significant reduction in sexual HSV-2 transmission with daily use of valcyclovir by the infected person. Suppressive therapy for early genital herpes addresses high initial levels of AVS, increased risk of GH transmission, and psychosocial problems associated with frequent clinical outbreaks.[5,32,33] ■

References

1. De Clercq E, Field HJ. Antiviral prodrugs—the development of successful prodrug strategies for antiviral chemotherapy. Br J Pharmacol. 2006;147:1-11.
2. Whitley RJ, Gnann JW Jr. Acyclovir: a decade later [published erratum appears in N Engl J Med. 1993;328:671. N Engl J Med. 1997;337:1703]. N Engl J Med. 1992;327:782-789.
3. Armstrong GL, Schillinger J, Markowitz L, et al. Incidence of herpes simplex virus type 2 infection in the United States. Am J Epidemiol. 2001;153:912-920.
4. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. Sex Transm Infect. 1999;75:3-17.
5. Corey L, Wald A, Patel R, et al, for the Valacyclovir HSV Transmission Study Group. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. N Engl J Med. 2004;350:11-20.
6. Corey L, Wald A, Celum CL, et al. The effects of herpes simplex virus-2 on HIV-1 acquisition and transmission: a review of two overlapping epidemics. J Acquir Immune Defic Syndr. 2004;35:435-445.
7. Freeman EE, Weiss HA, Glynn JR, et al. Herpes simplex virus 2 infection increases HIV acquisition in men and women: systematic review and meta-analysis of longitudinal studies. AIDS. 2006;20:73-83.
8. Xu F, Schillinger JA, Sternberg MR, et al. Seroprevalence and coinfection with herpes simplex virus type 1 and type 2 in the United States, 1988-1994. J Infect Dis. 2002;185:1019-1024.
9. Xu F, Sternberg MR, Kottiri BJ, et al. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. JAMA. 2006;296:964-973.
10. Fleming DT, McQuillan GM, Johnson RE, et al. Herpes simplex virus type 2 in the United States, 1976 to 1994. N Engl J Med. 1997;337:1105-1111.
11. ACOG Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 46. Gynecological herpes simplex virus infections. Obstet Gynecol. 2004;104:1111-1117.
12. Department of Health and Human Services, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2006. MMWR. 2006;55:1-94.
13. Langenberg AG, Corey L, Ashley RL, et al, for the Chiron HSV Vaccine Study Group. A prospective study of new infections with herpes simplex virus type 1 and type 2. N Engl J Med.1999:341:1432-1438.
14. Ashley RL. Laboratory techniques in the diagnosis of herpes simplex infection. Genitourin Med. 1993;69:174-183.
15. Slomka MJ, Emery L, Munday PE, et al. A comparison of PCR with virus isolation and direct antigen detection for diagnosis and typing of genital herpes. J Med Virol. 1998;55:177-183.
16. Wald A, Huang ML, Carrell D, et al. Polymerase chain reaction for detection of herpes simplex virus (HSV) DNA on mucosal surfaces: comparison with HSV isolation in cell culture. J Infect Dis. 2003;188:1345-1351.
17. Jerome KR, Huang ML, Wald A, et al. Quantitative stability of DNA after extended storage of clinical specimens as determined by real-time PCR. J Clin Microbiol. 2002;40:2609-2611.
18. Whittington WL, Celum CL, Cent A, et al. Use of a glycoprotein G-based type-specific assay to detect antibodies to herpes simplex virus type 2 among persons attending sexually transmitted disease clinics. Sex Transm Dis. 2001;28:99-104.
19. Ashley RL. Sorting out the new HSV type specific antibody tests. Sex Transm Infect. 2001;77:232-237.
20. Ashley-Morrow R, Krantz E, Wald A. Time course of seroconversion by HerpeSelect ELISA after acquisition of genital herpes simplex virus type 1 (HSV-1) or HSV-2. Sex Transm Dis. 2003;30:310-314.
21. Laderman EI, Whitworth E, Dumaual E, et al. Rapid, sensitive, and specific lateral-flow immunochromatographic point-of-care device for detection of herpes simplex virus type 2-specific immunoglobulin G antibodies in serum and whole blood. Clin Vaccine Immunol. 2008;15:159-163.
22. Miyai T, Turner KR, Kent CK, et al. The psychosocial impact of testing individuals with no history of genital herpes for herpes simplex virus type 2. Sex Transm Dis. 2004;31:517-521.
23. Catotti DN, Clarke P, Catoe KE. Herpes revisited. Still a cause of concern. Sex Transm Dis. 1993;20:77-80.
24. Gilbert L, Scanlon K, Peterson R, et al. Patient and partner perceptions about preventing genital herpes transmission. Herpes. 2005;12:60-65.
25. Bernstein DI, Lovett MA, Bryson YJ. Serologic analysis of first-episode nonprimary genital herpes simplex virus infection. Presence of type 2 antibody in acute serum samples. Am J Med. 1984;77:1055-1060.
26. Diamond C, Selke S, Ashley R, et al. Clinical course of patients with serologic evidence of recurrent genital herpes presenting with signs and symptoms of first episode disease. Sex Transm Dis. 1999;26:221-225.
27. Mertz GJ, Benedetti J, Ashley R, et al. Risk factors for the sexual transmission of genital herpes. Ann Intern Med. 1992;116:197-202.
28. Wald A, Zeh J, Selke S, et al. Virologic characteristics of subclinical and symptomatic genital herpes infections. N Engl J Med. 1995:333:770-775.
29. 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;190:1374-1381.
30. Data on file. GlaxoSmithKline. New York, NY.
31. Fife KH, Warren TJ, Ferrera RD, et al. Effect of valacyclovir on viral shedding in immunocompetent patients with recurrent herpes simplex virus 2 genital herpes: a US-based randomized, double-blind, placebo-controlled clinical trial. Mayo Clin Proc. 2006;8:1321-1327.
32. Carney O, Ross E, Bunker C, et al. A prospective study of the psychological impact on patients with a first episode of genital herpes. Genitourin Med. 1994;70:40-45.
33. Handsfield HH, Warren T, Werner M, et al. Suppressive therapy with valacyclovir in early genital herpes: a pilot study of clinical efficacy and herpes-related quality of life. Sex Transm Dis. 2007;34:339-343.