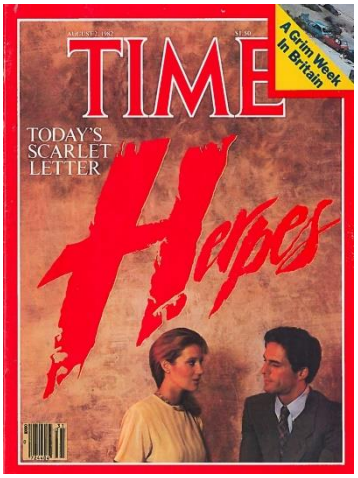
Genital Herpes Screening, Diagnosis, & Treatment: Knowledge is Power

Introduction

It's been nearly three decades since *Time* Magazine's memorable cover had the word "Herpes" emblazoned in red across the page with the caption "*Today's Scarlet Letter"* and a grim-faced, heavily clothed couple beneath it. Since then, the stigma remains, and the incidence of genital herpes has blossomed. The CDC estimates there are 50 million infected adults in the U.S., making this one of the most prevalent STIs.[1,2] Yet only one in 10 affected persons knows they have the infection, as many infected individuals have symptoms that have been attributed to other diagnoses. While the classic presentation of genital herpes is easier to diagnose, it is less common than the atypical presentation. The infection often recurs, and asymptomatic shedding is common. The disease is relatively easy to transmit to others, and transmission frequently occurs in the absence of symptoms. The diagnosis of herpes can result in significant physical and emotional consequences as well as potential harm to newborns. Since the *Time* article, effective pharmacologic therapy has become available but can only be offered to patients if the diagnosis is made, which is why it is essential that healthcare practitioners are aware of who, when, and how to screen.



Herpes Epidemiology[2-7]

Herpes simplex 1 (HSV-1), or "oral herpes," causes cold sores or fever blisters. Initial oral infections frequently occur in childhood with the majority of adults exhibiting antibodies to the virus. The virus often recurs around the lips or facial area frequently associated with stress or illness. Persons may contract HSV-1 in the genitals by oral or other anogenital sex. About 30% to 50% of newly diagnosed primary genital HSV infections are Type 1. Reinfection infrequently recurs or sheds from the genitals after the first infection and carries less long-term implications. However, contracting HSV-1 infection late in pregnancy can cause a severe neonatal herpes infection.

Herpes simplex 2 (HSV-2) causes genital herpes infections with significant symptoms; it can recur in "non-genital" sites below the waist and result in severe neonatal infections. Though there is the possibility of acquiring a primary HSV-2 infection in the mouth with oral sex, it rarely will recur in that site. Contracting primary HSV-2 infection late in pregnancy can cause a severe neonatal herpes infection.

Data from the 2005-2010 National Health and Nutrition Examination Survey indicate that the prevalence of HSV-2 infection ranges from 1.2% in adolescents aged 14 to 19 years to 25.6% in adults aged 40 to 49 years; the prevalence in women is twice that of men.[8] HSV becomes dormant in the body after the initial infection only to later reactivate or cause asymptomatic shedding and transmission to others.

Clinical Presentation of HSV[2-12]

A primary episode occurs on first infection with the virus in the absence of circulating antibodies. Any symptomatic episode after the development of antibodies is considered a recurrence. The appearance of primary genital herpes infection is quite characteristic, first starting as vesicles and then becoming painful ulcerations and sores in the genital region. Sores or ulcerations can cause dysuria, itching, discharge, and local lymphadenopathy, which is associated with malaise, fever, headache, and fatigue. This may last 2 to 3 weeks if not treated. However, most primary infections are asymptomatic or minor and cause internal genital lesions that are not recognized. Persons with prior oral HSV-1 infection may exhibit minimal symptoms because of the ameliorating effects of their HSV-1 antibodies. Even though HSV-1 antibodies do not protect against infection with HSV-2, they can modify the symptomatic response to HSV-2 infection.

After the initial infection, the virus retreats down the sensory nerves and sets up residence in the lower spine ganglia. Later, the virus may travel back up the sensory nerves and cause symptoms in genital or extragenital sites, such as the lower abdominal wall, rectum or anus, buttocks, or thighs. Genital recurrences are almost always due to HSV-2. The diagnosis of a primary infection requires simultaneous serologic testing for HSV antibodies. Occasionally, a severe episode with systemic symptoms may actually be a recurrence, in which the primary episode was either asymptomatic or presented as a minor lesion without symptoms.

The 2015 CDC STD Guidelines state: "*Most persons infected with HSV-2 have not had the condition diagnosed. Many such persons have mild or unrecognized infections but shed virus intermittently in the anogenital area. As a result, most genital herpes infections are transmitted by persons unaware that they have the infection or who are asymptomatic when transmission occurs.[1]*"

Occasionally, HSV causes lesions or infections of the fingers [a Whitlow]. HSV-1 is the cause in approximately 60% of cases of herpetic whitlow, and HSV-2 is the cause in the remaining 40%. Although it is more rare, infections can also occur on the cornea or in the nervous system. Infants can be infected in utero or at delivery if significantly exposed to the virus. Neonatal infections can cause meningitis, blindness, and even death.

Diagnosis

Most primary infections go unrecognized. Recurrences may be erroneously diagnosed as recurrent yeast or UTI, shaving irritation, sexual friction, or allergy to latex or soap. Recurrences may look like an abrasion or fissure, either of which should be considered herpes until proven otherwise. There may only be itching or vaginal discharge with no obvious lesions or only introital or labial redness. Anal symptoms are often attributed to hemorrhoids or pinworms, and skin lesions on the thighs, abdomen, or buttocks are often diagnosed as furuncles, ingrown hairs, spider bites, poison ivy, or heat rash.[13] Genital herpes needs to be included in differential diagnosis of any recurrent genital or regional cutaneous symptoms.

Images 1-6 below, illustrate various episodes of HSV:

First Episode Primary HSV

- The patient presented with complaints of severe pain and burning upon urination. She had a fever of 103º F, headache, and malaise.
- Examination revealed multiple tender ulcers bilaterally. One cannot visually distinguish between HSV-1 and HSV-2. The culture yielded a positive result for HSV-1. This is a typical first episode primary herpes outbreak with associated constitutional symptoms.

First Episode – Non-primary HSV

- The patient is a 20-year old female presenting with tender ulcers of 2 days duration.
- The patient gave no past history of genital herpes outbreaks. The culture was positive for HSV-2, and HSV-2 antibodies were detected on laboratory analysis. The patient likely suffered from a previous asymptomatic acquisition of HSV-2, and this is her first recognized herpes outbreak.

Recurrent HSV

- The patient had been shaving her genital area regularly over the past year. She first noticed an area of irritation 7 months ago. This was the third time she had these sores in the same spot, which she had thought was the result of her shaving. The patient saw her physician who cultured the sores. The culture was positive for HSV-2. This is a typical episode of recurrent HSV.

Recurrent HSV

- The patient had been complaining of intermittent episodes of anal pain and itching for the past 7 months. She had been treating herself for hemorrhoids.
- An examination revealed unilateral tender perianal ulcers, which were culture positive for HSV-2. Though not acquired anally, the recurrences are occurring in the distribution of the involved nerve distribution.

Atypical Presentation – Excoriation

- The patient presented to her gynecologist stating that she had cut herself while scratching with her fingernails 1 day before.

- While this may look like a traumatic excoriation, the culture was positive for HSV-2. Six months before, the patient had a bilateral primary genital herpes outbreak. This is her first recurrence. It is important to remember that all genital excoriations should be evaluated for HSV.

Atypical Presentation – Erythema

- The patient complained of vulvar pain and redness of 2 days duration. Examination revealed bilateral erythema of the vulva. Her physician initially made the diagnosis of vulvar candidiasis.
- On occasion, genital herpes may present with only erythema. There may be no vesicles, pustules, or ulcers. In this case, there was no yeast present, but a culture taken from the highlighted fissure was positive for HSV-2.

Atypical Recurrent HSV

- The patient had been to her doctor 3 times over the past 8 months with a pruritic and mildly painful rash on her right buttock. She had been told that it was an irritation from riding a bicycle. She initially thought it was a spider bite.

- This outbreak reveals grouped ulcers on an erythematous base. The culture was positive for HSV-2. Because of the atypical location of the outbreak, a diagnosis of genital herpes had not been considered.

Laboratory Methods

The CDC states[1] "the clinical diagnosis of genital herpes is both insensitive and nonspecific." The WHO concurs and states, in part:[14]

Laboratory methods for the diagnosis of HSV-2 [and differentiation from HSV-1) include direct detection from lesions and indirect serological methods. Available tests include antigen detection, isolation of virus by culture, and nucleic acid amplification tests (NAATs) for viral DNA. Serological assays are also available to screen by detection of type-specific antibodies, which develop in the first several weeks after initial infection and persist indefinitely.

As alluded to, HSV culture was long considered the gold standard for testing of a visible lesion. However, there is a high false-negative rate if inadequate numbers of viral particles are being shed. Polymerase chain reaction (PCR) testing for the presence of HSV DNA is significantly more sensitive than culture and routinely differentiates between HSV-1 and HSV-2. Although a positive culture or PCR is definitive, a negative test does not rule out herpes. Cytology is not helpful.[1,15-17] For type-specific HSV-1 and HSV-2 IgG tests, the CDC notes that false negatives are more likely in the early stages of infection.[1] By contrast, herpes IgM testing is not useful. Western Blot testing is considered the gold standard of serologic testing. The Aptima HSV-1 and 2 assay qualitatively detects and differentiates between HSV-1 and HSV-2 (Hologic; San Diego, CA). The assay is a NAAT for the qualitative detection and differentiation of HSV-1 and HSV-2 in clinician-collected swab specimens from anogenital skin lesions. Specimens collected in a broad range of transport media, including the Aptima specimen transport medium, can be tested with the assay.[1,6,18-22] NAATs are increasingly preferred due to higher sensitivity, ease of specimen collection and transportation, and faster results.[14]

Patient Counseling

Most patients diagnosed with herpes react with shock and disbelief, though some respond with less surprise because they had wondered if they had a herpes infection due to prior known exposures or symptoms. Often, patients want to know when, how, and why. Much of the management of a herpes diagnosis involves helping them learn about their infection, answering those questions that can be answered, and explaining those that cannot. There are often misconceptions about the diagnosis as well, such as that viral infection causes cancer (it does not) or that it means they can never have children or deliver vaginally (untrue). Patients also often fear that they will never be able to have a normal sex life or have another intimate relationship (also untrue). There may be anger at having become infected, and there are appropriate fears about transmission to future partners. This is why counseling and

education are vitally important. Patients should be advised about partner notification, risk of asymptomatic viral shedding and transmission, and dispelling misconceptions. Patients also need to be informed that there are effective and safe medications available that not only help treat and control the infection, but also reduce the risk of transmission to an uninfected partner. Additional education on appropriate use of condoms should be provided, and excellent websites and hotlines are available for patient education as well as written materials.

USPSTF Statement on Screening

In 2016, the USPSTF published a statement on HSV testing.[3,23] It noted that "genital herpes is a prevalent sexually transmitted infection in the United States, occurring in almost 1 in 6 persons aged 14 to 49 years" and "reviewed the evidence on the accuracy, benefits, and harms of serologic screening for HSV-2 infection in asymptomatic persons, as well as the effectiveness and harms of preventive medications and behavioral counseling interventions to reduce future symptomatic episodes and transmission to others."

The USPSTF concluded "that the harms outweigh the benefits for population-based screening for genital HSV infection in asymptomatic adolescents and adults, including those who are pregnant, largely based on concerns about the risk of a false positive screen with the currently available tests (specificity) and the potential anxiety and disruption of personal relationships related to diagnosis." They recommended "further development of screening and diagnostic tests with higher specificity that detect both asymptomatic genital HSV-1 and HSV-2 infections."

The USPSTF also recommended "intensive behavioral counseling interventions to reduce the likelihood of acquiring an STI for all sexually active adolescents and for adults at increased risk." It then acknowledged that "persons with genital herpes can spread the infection to sexual partners even when they are asymptomatic." Studies suggest that up to 85% of persons who are found to be infected with HSV-2 and who report no prior symptoms of genital herpes have a symptomatic outbreak within 6 months of being tested. Patients who receive education about genital herpes may be more likely to recognize and report its symptoms. Some patients who are considered 'asymptomatic' may have actually experienced symptoms but are not aware they have a genital herpes infection.

Treatment[24-32]

The mainstay of therapy is antiviral medications, including acyclovir, valacylovir, and famciclovir, that interact with viral thymidine kinase and stop viral replication. Each drug has a specific dose range for treatment primary episodes, recurrent episodes, and suppression of recurrences.[1] Recommendations for patient treatment and counseling can be accessed via the CDC website at: https://www.cdc.gov/std/tg2015/herpes.htm

Summary

Some healthcare practitioners are hesitant to provide testing for herpes. The concern is the belief that patients are better off not knowing they have been infected because of the associated emotional issues

and stigma. However, what a patient does not know *can* be detrimental because knowledge is power. With an accurate diagnosis, appropriate treatment can be provided for typical as well as atypical presentations. In addition, an accurate diagnosis prevents misdiagnoses, unnecessary treatments, and potential transmission to others or to newborns. Thanks to diagnostic advances, genital HSV-1 infections can be differentiated from genital HSV-2 infections, and appropriate counseling can—and should—be provided to patients, who expect to receive an accurate diagnosis with appropriate therapy, even when it may involve emotional distress or awkwardness on their part or the provider's. Informing patients about their HSV status is essential when performing STD screens. Patients should be advised of the risk of false positive serologic testing, that results need to be interpreted carefully, and if necessary, confirmed with additional testing. Infection with HSV-2 is the most prevalent STD. If both HSV-1 and HSV-2 serologic screening is not performed when a patient requests STD testing, the patient should be fully informed to ensure they do not erroneously inform partners that they have been screened for "everything."

Case Studies from the Author's Practice

- Stacy is a 19-year-old co-ed who developed painful ulcerations on her vulva and was told by the student health service that she had genital herpes, later confirmed by culture. She is quite distressed by this diagnosis since she has not yet had intercourse. She has been the recipient of oral sex from a partner with no history of oral lesions. The lab serotyped a frozen specimen and on request did typing which showed HSV-1. Her boyfriend was positive for HSV-1 on serologic testing and negative for HSV-2. She tested negative for both on blood testing, confirming the diagnosis of primary genital HSV-1. She responded to antiviral therapy and has had no recurrences. She also is quite relieved by the diagnosis of "oral" HSV in the genitals, believing she "does not have genital herpes" that may recur or be transmitted.

- Angela is 30 years old, 35 weeks into her first pregnancy and presents with painful vulvar ulcerations with systemic symptoms suggestive of a new herpetic infection. Culture is positive for HSV-2. She has had no history of prior gynecologic problems other than episodic recurrent yeast and urinary tract infections during earlier years. Her husband has no history of herpes but has had rare "pimples" on his penis in the past with occasional "jock itch." Her obstetrician initially counseled her about the significant risk associated with primary herpes late in pregnancy. She was placed on a 10-day antiviral course. Her antibody screen was positive for HSV-2, suggesting an atypical severe recurrent outbreak and supporting the conclusion that her earlier milder recurrent genital symptoms were herpetic. Her husband's serology was also positive, making transmission unclear. Angela was treated for the outbreak and placed on prophylactic acyclovir for the balance of her pregnancy. Because she had antibodies, her risk of neonatal transmission was felt to be low in the absence of lesions. Angela had an uncomplicated vaginal delivery with no HSV recurrences or neonatal consequences. Her severe first clinical HSV manifestation is felt to be the consequence of alterations of immunity by the pregnancy.

- 23-year-old Mary came for a routine Pap test. Upon examination she was noted to have an abrasion between the left labia minora and majora. The patient stated these abrasions resulted

from recent shaving due to a new relationship. A viral culture was positive for HSV-2 and her antibody screen was negative. These findings suggest a primary infection with an atypical presentation likely modified because HSV-1 antibodies were found to be present.

- Karlin, 35 years old, has a periodically recurring sore on her right buttocks. The lesion appears as a cluster of spider bites. Thorough house cleaning and a visit by the exterminator failed to resolve the problem. A culture taken during an episode was negative, but PCR was positive for HSV-2, as was Karlin's type-specific antibody screen.

- Janice is a 22-year-old newlywed who presented with fever, chills, malaise, and severe ulcerations covering her vulva, vagina, and cervix. Her cervix is swollen to twice its normal size and fragments upon touching. She is unable to void due to edema of the labia and periurethral tissues. Pathology on a cervical fragment shows marked inflammation. There is profuse exudate from the vagina. History reveals recent oral sex. Her husband reported an oral cold sore on the next day. She was admitted, and a foley catheter was placed to allow for voiding. She was treated with IV acyclovir. Her HSV culture was positive for HSV-1 and *Staphylococcus aureus*. In the next 24-48 hours, she developed liver function abnormalities and cutaneous sloughing consistent with toxic shock syndrome. Additional antibiotics were administered, and she responded to treatment. She has had a complete recovery and 2 subsequent uncomplicated vaginal births with no apparent recurrence.

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