

Genital and Perirectal Herpes Simplex Virus Infection

Learning Objectives

Upon completion of this module, the learner will be able to:

1. Discuss current incidence and prevalence rates of genital HSV.
2. Describe the pathogenesis and clinical manifestations of genital HSV.
3. Explain the application of current diagnostic tests, given a specific case example.
4. Discuss the therapeutic strategies for genital HSV.
5. Deliver appropriate counseling messages based on current transmission and treatment information.
6. Discuss the relationship between HSV and HIV infection.

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I. Epidemiology

A. The virus:

1. A member of the human herpes viruses (herpetoviridae), which include: HSV-1, HSV-2, VZV, EBV, CMV, HHV-6, HHV-7, HHV-8.
2. A double-stranded DNA virus surrounded by an envelope of lipid glycoprotein.
3. 50% DNA homology between HSV-1 and HSV-2.
4. All members of this species establish latent infection in specific target cells.
5. Infection persists despite the host immune response, often with recurrent disease. Re-infection can occasionally occur despite immunity.

B. The majority of genital and perirectal herpetic outbreaks in the U.S. are caused by HSV-2, although up to 10-50% of first episodes are due to HSV-1.

C. Routes of transmission are sexual (genital to genital and oral to genital) and perinatal (mother-to-child).

D. It is estimated that at least one million new cases occur each year; 50% or more of new cases are asymptomatic or unrecognized.

E. In the general U.S. population, 22% of adults over age 12 have HSV-2 antibodies. Among whites, 15% of men and 20% of women are HSV-2 seropositive, and among blacks, 35% of men and 55% of women are seropositive; seropositivity increases with age.

F. HSV-2 seroprevalence rates show a correlation with level of sexual activity (prostitutes 80%, nuns 3%).

G. Seropositivity to HSV-2 is higher in HIV-infected persons and adults of lower socioeconomic status.

H. Most sexual transmission occurs while the source contact case is asymptomatic.

- I. The risk of sexual transmission is difficult to quantify, but is estimated at 10% per year in recent studies of monogamous heterosexual couples with discordant HSV serum antibody status.
- J. Efficiency is greater from men to women than from women to men (17% vs. 4%), and the presence of serum antibody to HSV-1 may be partially protective against acquisition of infection. HSV-1 seropositivity partially protects against having a symptomatic infection.
- K. Likelihood of transmission (frequency of occurrences and asymptomatic viral shedding) to others declines with increased duration of infection.
- L. Incubation period after acquisition is 2-12 days (average is 4 days).
- M. HSV is readily inactivated by drying and soap and water, so that fomite transmission is unlikely.
- N. There is mounting evidence that genital HSV-2 infection facilitates both acquisition and transmission of HIV infection.

II. Pathogenesis

- A. Mucosal inoculation (in genital infection)--> virus is transported along peripheral nerve axons to the nerve cell bodies' sacral ganglia.
- B. Virus remains latent indefinitely in the paraspinal ganglia.
- C. Reactivation, precipitated by multiple known factors (trauma, fever, UVL, stress, etc.) and unknown factors, induces viral replication.
- D. The re-activated virus migrates centrifugally to mucosal surfaces by way of the peripheral sensory nerves, where it may cause a cutaneous outbreak of herpetic lesions.
- E. Histopathologic changes include focal necrosis, ballooning degeneration of cells, production of mononucleated giant epithelial cells, and eosinophilic intra-nuclear inclusions called Cowdry type A bodies.

- F. Up to 90% of persons seropositive for HSV-2 antibody have no clinical history of anogenital herpes outbreaks. However, most have mild unrecognized disease and probably all shed virus from the genital area intermittently.

III. Clinical Manifestations

A. Definitions of types of infection:

1. First clinical episode:
 - a) Primary infection:
 - 1) First infection ever with either HSV-1 or HSV-2.
 - 2) No serum antibody present when symptoms appear.
 - 3) Disease is more severe than recurrent disease.
 - 4) Serum antibody appears in convalescence.
 - b) Non-primary infection:
 - 1) Newly acquired infection with HSV-1 or HSV-2 in an individual previously seropositive to the other virus.
 - 2) Manifestations tend to be milder than primary infection.
 - 3) Cross-reacting antibody is present initially and may rise in convalescence. Type-specific antibody appears and rises in convalescence.
 - 4) Twenty-five percent of patients with first clinical episode of HSV-2 have had a prior asymptomatic primary infection. Type-specific antibody will be present when the patient presents and the severity of the episode is comparable to a recurrence (first episode, recurrence).
2. Recurrent symptomatic infection:
 - a) Antibody is present when symptoms appear, although the patient may not be aware of previous episodes.
 - b) Generally, there is no or little change in antibody titer in convalescence. Disease is usually mild and short in duration.
3. Asymptomatic infection:
 - a) Serum antibody is present:
 - b) There is no known history of clinical outbreaks.
 - c) Up to two-thirds of patients with identified asymptomatic HSV-2 infection can be taught to recognize clinical signs and symptoms of genital herpes.

Infection Type	Lesions/Symptoms	Type Specific Antibody At Time of Presentation	
		HSV-1	HSV-2
First episode Primary Type 1 or 2	+/Severe, bilateral	-	-
First episode Non-primary Type 2	+/Moderate	+	-
First episode Recurrence Type 2	+/Mild	+/-	+
Symptomatic Recurrence Type 2	+/Mild, unilateral	+/-	+
Asymptomatic Infection Type 2	-	+/-	+

B. Clinical Manifestations

1. Primary (initial) infection without treatment: characteristic picture is that of multiple lesions that are more severe, last longer, and have higher titers of virus than recurrent infections. Start as papules → vesicles → pustules → ulcers → crusts → healed. Illness lasts 2-4 weeks.
 - a) Often associated with systemic symptoms, including fever, headache, malaise, myalgia (40% men, 70% women); urinary retention in 10% of women.
 - b) Systemic symptoms peak within 3-4 days of onset of lesions and gradually recede over the next 3-4 days.
 - c) Local symptoms are predominantly pain (95%), itching, dysuria (60%), vaginal (85%) or urethral (30%) discharge, and tender inguinal adenopathy (80%).
 - d) Painful genital lesions that are numerous and bilateral; last an average of 11-12 days; full re-epithelialization takes an average of 17-20 days.
 - e) Median duration of viral shedding (from the onset of lesions to the last positive culture) is ~12 days, and correlates well with the mean time from the onset of vesicles to crusting.

- f) Inguinal adenopathy peaks in week 2-3 and is often the last finding to resolve. Nodes are firm, nonfluctuant, and tender to palpation. Suppuration is rare.
 - g) Primary HSV cervicitis occurs in ~90% of primary HSV-2 infection and ~70% of primary HSV-1 infections. It may manifest as a mucopurulent cervicitis, or it may be asymptomatic. The cervix will appear abnormal to inspection in the majority of cases, with ulcerative lesions, erythema, or friability. Clinical differentiation from gonorrheal or chlamydial cervicitis may be difficult, although cervical ulceration may suggest HSV.
 - h) The exo-or endocervix may be involved.
2. Recurrent infection without treatment. Illness lasts 5-10 days:
- a) Prodromal symptoms (localized tingling, irritation) in ~50% begin 12-24 hours before lesions and sometimes without lesions ("false prodrome").
 - b) Duration is shorter than in primary infection: painful genital lesions last 4-6 days; average duration of viral shedding 4 days.
 - c) Lesions tend to be unilateral.
 - d) Symptoms tend to be milder and less severe. Usually there are no systemic symptoms.
 - e) Rate of cervical virus shedding in women is 12-20%.
 - f) Average of 2-6 recurrences/year, but highly variable.
 - g) HSV-2 primary infection is much more prone to recur than HSV-1 primary infection.
 - h) HSV-2 will recur slightly more frequently and after shorter period of time in men than in women; median five recurrences per year compared with four in the first year of infection.
 - i) Recurrences are more frequent if the primary episode is prolonged >30 days.
3. Asymptomatic viral shedding:
- a) Most HSV-2 is transmitted during asymptomatic shedding.
 - b) Has been documented in almost all HSV-2 seropositive persons studied. Rates were greatest in the first 3 months, and then declined.
 - c) Asymptomatic shedding is of briefer duration than during clinical recurrences.
 - d) Rates of asymptomatic shedding are greater with HSV-2 than HSV-1.
 - e) Presence of serum antibody of HSV-1 seems to decrease rates of asymptomatic shedding with HSV-2.

- f) Asymptomatic shedding occurs less frequently in women with established HSV-2 infection (mean: 4% of days). Up to 5-10% of days in those with newly acquired infections (<2 years).
- g) Asymptomatic shedding as detected by PCR present on 28% of days (range 0 to 77%).
- i) Shedding dramatically reduced, although not eradicated by acyclovir chemosuppression.
- j) In a recent study, the rate of subclinical shedding in patients with no reported history of genital herpes was similar to that in patients with such a history (3.0% vs. 2.7%).
- k) Vulva and perianal areas in women and penile skin and perianal area in men are the most common sites of asymptomatic shedding.

C. Complications of genital infection:

1. Aseptic meningitis:
 - a) More common in primary than in recurrent infection.
 - b) More common with HSV-2 than HSV-1.
 - c) More common in women than in men (36% of women with primary HSV-2 infection versus 11% of men).
 - d) May be severe, requiring hospitalization and/or parenteral narcotics.
 - e) There are generally no neurologic sequelae; however, recent data suggest that benign recurrent meningitis (Mollaret's meningitis) is usually caused by HSV-2.
2. Other (rare):
 - a) Stomatitis and pharyngitis.
 - b) Radicular pain, sacral paresthesias.
 - c) Transverse myelitis.
 - d) Autonomic dysfunction: hyperesthesias, neurogenic bladder, constipation, and impotence.
 - e) Disseminated (viremic) infection: occasional in patients with atopic eczema, pregnant women, impaired CMI, neonates. Can be a cause of fulminant hepatitis in immunosuppressed patients.
 - f) Ocular involvement (more common with HSV-1).
 - g) Herpetic whitlow (more common with HSV-1).

IV. Diagnosis

A. Viral culture (gold standard):

1. Highly specific (>99%) and sensitive, but not as sensitive as PCR.
2. Viral recovery depends on stage of lesion and proper collection technique; vesicles: 90%, ulcers: 70%, and crusted lesions: 30% culture more commonly positive in primary infection (80: 90%) as contrasted with recurrences (30%).
3. Time limitations: most will be positive within 24-72 hours, but are generally held for 5-7 days.
4. Stable in viral transport media for 48-72 hours at 4°C.
5. Allows for easiest typing (I vs. II).

B. Antigen detection (DFA or EIA):

1. Fairly sensitive (>85%) in symptomatic shedders.
2. Rapid (2-12 hours).
3. Highly specific; can differentiate HSV-1 from HSV-2 or VZV using monoclonal antibodies, but false positives can occur.
4. May be better than culture for healing lesions.

C. Cytology (Tzank or Pap):

1. Identifies typical HSV-infected cells (multi-nucleated giant cells and eosinophilic inclusion bodies) in exfoliated cells or biopsies.
2. Insensitive (50%).
3. Nonspecific (cannot differentiate HSV from VZV).

D. PCR. highly sensitive and specific. Clinical significance of a positive result in process of being established.

E. Serologic tests:

1. The older serological tests (CF, IFA, EIA) did not distinguish between HSV-1 and HSV-2 antibody.
2. New serological tests using antigens specific for HSV-1 (gG1) and HSV-2 (gG2) and EIA and Western blotting (WB) methods have been developed and are now commercially available for type-specific testing. Currently the FDA-approved gG-based type-specific assays include: Diagnology POCKit™ HSV-2, Focus Technology, Inc HSV-1 or HSV-2 gG ELISA, and HSV-1 and HSV-2 Differentiation Immunoblot. The POCKit™-HSV2 assay is a point-of-care test that provides results for HSV-2 antibodies from capillary blood or serum during the clinic visit. The Focus Technology assays are laboratory-based. The sensitivities of these tests for detection of HSV-2 antibody vary from 80% to 98% and false-negative results may occur, especially early after infection. The specificities of these assays are $\geq 96\%$; false-positive results can occur, especially in patients with low likelihood of HSV infection. Therefore, repeat testing or a confirmatory test (e.g., an immunoblot assay if the initial test was an ELISA) may be indicated in some settings.
3. Potential uses of new serological tests:
 - a) Diagnosing recurrent genital lesions or atypical genitourinary symptoms.
 - b) Counseling couples in which one of the pair has genital herpes and the other does not know or is unsure. This might be particularly valuable in planning pregnancy or pregnant couples.
 - c) Screening in selected high-risk populations such as in STD clinics. Cost-benefit analyses have not been performed comparing the costs of the tests vs. the savings resulting from preventing further cases. While serologic assays from HSV-2 should be available for persons who request them, screening for HSV-1 or HSV-2 infection in the general population is not indicated.

F. Special diagnostic considerations:

1. Establish the etiology of atypical genital ulcer(s) to include mixed infections (e.g., syphilis and chancroid) and unusual infections (e.g., LGV, HIV, CMV) and other causes (e.g., cancer).
2. Evaluate for acyclovir resistance in patients with persistent genital herpes despite antiviral suppressive therapy.

V. Treatment (See Current CDC Treatment Guidelines)

A. Antiviral therapy for uncomplicated HSV:

1. Basic pharmacology of current medications:
 - a) Acyclovir (ACV).
 - b) Valacyclovir.
 - c) Famciclovir.

B. Present use of antivirals in therapy of genital/perianal HSV:

1. Topical medication: therapeutic effect of topical acyclovir in normal hosts is not better than placebo.
2. Recommended oral regimens for treatment of initial clinical episode:
 - a) Dramatic effect in initial HSV infection, especially if symptoms <7 days and no history of oral HSV.
 - b) Acyclovir 400 mg t.i.d. for 7-10 days until complete crusting has occurred. Acyclovir 200 mg 5 times daily also effective, but compliance is difficult.
 - c) Valacyclovir 1 gm b.i.d. for 7-10 days.
 - d) Famciclovir 250 mg t.i.d. for 7-10 days.
 - e) Treatment may be extended if healing is incomplete after 10 days of therapy.
 - f) Acyclovir 400 mg 5 times daily in HIV-infected patients or for herpes proctitis or oral stomatitis.
 - g) Valacyclovir and famciclovir are likely to be effective for HSV proctitis or oral infection, but clinical experience is lacking.

- h) Factors to weigh when considering treatment: severity of symptoms, immune status, pregnancy, history of complications, and cost.
3. Intravenous medication:
 - a) For use in severe primary infection, complications such as urinary retention secondary to sacral radiculitis, aseptic meningitis or in progressive or invasive mucocutaneous HSV.
 - b) Dose: acyclovir 5-10 mg/kg every 8 hours. After clinical improvement, oral administration of acyclovir, valacyclovir or famciclovir is recommended for a total of 10 days.
 4. Recommended regimens for treatment of episodic recurrent infection:
 - a) Acyclovir 400 mg orally 3 times a day for 5 days, or 200 mg 5 times a day for 5 days, or 800 mg twice a day for 5 days; famciclovir 125 mg orally twice a day for 5 days or valacyclovir 500 mg twice a day for 3-5 days or valacyclovir 1.0 gm once a day for 5 days. A 3-day course of valacyclovir 500 mg twice daily has been shown to be as effective as a 5-day course. Similar studies have not been done with acyclovir and famciclovir.
 - b) In recurrent HSV, therapy shortens virus shedding and lesion and symptom duration. Therapy appears to have no effect on interval until recurrence or frequency of recurrences. Patient should self-start the medication.
 5. Prophylaxis or suppression of HSV infection:
 - a) Indicated for persons with frequent recurrences (≥ 6 per year) or with complications like aseptic meningitis or sacral radiculitis.
 - b) Proven to decrease the frequency and severity of recurrent outbreaks by 75-80%.
 - c) Acyclovir has been used safely for up to 10 years and with valacyclovir and famciclovir for 1 year.
 - d) Dose: acyclovir 400 mg b.i.d.; valacyclovir 500 mg once daily or 1,000 mg once daily; and Famciclovir 250 mg b.i.d. Valacyclovir 500 mg once a day appears less effective than other valacyclovir dosing regimens in patients who have very frequent recurrences (i.e. >10 episodes per year).
 - e) Use continuously for 1 year, and then discuss discontinuation in order to reassess rate of recurrent episodes. Patients should be warned that they may have rebound outbreaks when suppression is discontinued; suppression does not eliminate ganglionic latency.

C. Episodic and suppressive therapy in HIV infection:

1. Episodic: acyclovir 400 mg t.i.d. for 5-10 days, or acyclovir 200 mg 5 times a day for 5-10 days, or famciclovir 500 mg orally b.i.d. for 5-10 days, or valacyclovir 1000 mg b.i.d. for 5-10 days.
2. Suppressive: acyclovir 400-800 mg b.i.d. or t.i.d; or famciclovir 500 mg b.i.d. or valacyclovir 500 mg b.i.d.
3. For severe cases, it may be necessary to initiate therapy with acyclovir 5-10 mg/kg IV every 8 hours.

D. Therapy of complicated HSV infection:

1. In acyclovir resistant HSV infections, sodium phosphonoformate (Foscarnet) intravenously is considered the therapy of choice.
2. To suppress recurrent episodes of Acyclovir resistant HSV in immunosuppressed patients, once or twice weekly Foscarnet injections may be necessary.
3. Cidofovir gel is currently under investigation and is not available presently for use.

E. Adjunctive therapy:

1. Pain relief: usually necessary only in primary disease. Painful urination can be alleviated by urinating in warm bath.
2. Topical measures: drying or analgesia is of unproven benefit, but some patients report relief.
3. Sitz baths.

VI. Prevention

A. Partner management:

1. Sex partners are likely to benefit from evaluation and counseling. Symptomatic sex partners should be evaluated and treated in the same manner as patients who have genital lesions. Asymptomatic sex partners of patients who have genital herpes should be questioned concerning histories of genital lesions, counseled to recognize symptoms of herpes, and offered type-specific serologic testing for HSV infection.
2. Sex partners of infected persons should be advised that they might be infected even if they have no symptoms. Type-specific serologic testing of asymptomatic partners of persons with genital herpes can determine whether risk of HSV acquisition exists.

B. Patient counseling and education:

1. Nature of the infection
 - a) Discuss natural history of the disease with emphasis on the potential for recurrent episodes, asymptomatic viral shedding, and sexual transmission.
 - b) Patients having a first episode of genital herpes should be advised that suppressive and episodic antiviral therapy is available and effective in preventing or shortening the duration of recurrent episodes.
 - c) Persons with genital herpes should be informed that sexual transmission of HSV can occur during asymptomatic periods. Asymptomatic viral shedding is more frequent in genital HSV-2 infection than in genital HSV-1 infection, and is most frequent in the first 12 months after acquisition of HSV-2.
 - d) Frequency of outbreaks generally decreases with increasing duration of infection.
 - e) Teach patients about prodromal symptoms and when/how to take medication.
 - f) Reduce events that trigger recurrences (e.g., stress).
 - g) Asymptomatic persons diagnosed with HSV-2 infection by type-specific serologic testing should receive the same counseling messages as persons with symptomatic infection. In addition, such persons should be

taught about the common manifestations of genital herpes, as many will become aware of them with time. Antiviral therapy is not recommended for persons without clinical manifestations of infection.

2. Transmission issues: counseling for the patient and regular sexual contacts:
 - a) Discuss history of disease with emphasis on potential for recurrent episodes, asymptomatic viral shedding, and sexual transmission.
 - b) Patients should be advised to abstain from sexual activity with uninfected partners when lesions or prodromal symptoms are present.
 - c) All persons with genital HSV infection should be encouraged to inform their current sex partners that they have genital herpes, and to inform future partners before initiating a sexual relationship.
 - d) Transmission can occur without lesions and most cases are transmitted during asymptomatic periods. Asymptomatic shedding is more common with HSV-2 and in those with recently acquired HSV.
 - e) Risk of neonatal infection should be explained to all patients, including men. Pregnant women and women of childbearing potential who have genital herpes should be advised to inform the health care providers who care for them during pregnancy as well as the providers who will care for their newborn infant.
 - f) Pregnant women without HSV-2 infection should be advised to avoid intercourse with men with genital herpes during their third trimester. Similarly, women without HSV-1 infection should be counseled to avoid genital exposure to HSV-1 during the third trimester (e.g., cunnilingus with a partner with oral herpes, and vaginal intercourse with a partner with genital HSV-1 infection).

3. Risk reduction:
 - a) Assess client's behavior-change potential.
 - b) Discuss prevention strategies (abstinence, monogamy, condoms, limit number of sex partners, etc.). Genital ulcer diseases can occur in both male or female genital areas that are covered or protected by a latex condom, as well as in areas that are not covered. Correct and consistent use of latex condoms can reduce the risk of genital herpes only when the infected area or site of potential exposure is protected.
 - c) Develop individualized risk-reduction plans.

4. Other: efficacy of determining type-specific HSV serostatus in high-risk groups has not yet been shown to be cost-effective in terms of preventing further cases.

VII. Special Considerations

A. Proctitis:

1. Symptoms of pain, discharge, tenesmus, constipation with or without symptoms of autonomic dysfunction.
2. Severe ulceration may be seen on anoscopy.

B. Urinary involvement:

1. Men with first-episode HSV have a positive urethral culture in 33% of cases and in first episode of primary genital herpes urethritis may be part of the clinical syndrome and may cause a clear mucoid discharge.
2. HSV has been isolated from ~5% of women with the dysuria-frequency syndrome.

C. Herpes in pregnancy:

1. In vaginal delivery, transmission occurs in <1% of recurrent genital herpes and up to 30-50% of infections acquired around the time of delivery.
2. Risk factors for HSV transmission to the infant include: new infection, primary infection, lack of type-specific antibodies, and scalp electrodes.
3. Prodrome or active lesions at the onset of labor: abdominal delivery is recommended.
4. Prevention must center on avoiding acquisition of HSV in late pregnancy. The new type-specific serologies may be of use in determining risk status and management of HSV in pregnancy.

5. Routine administration of acyclovir during pregnancy is not recommended. Use for life-threatening infection or severe primary outbreak during pregnancy. The risk of neonatal herpes is high in women who acquire genital HSV in late pregnancy, and such women should be managed in consultation with an expert. Some experts recommend acyclovir therapy in this setting, and some recommend routine caesarian section to reduce the risk of neonatal herpes or both. Acyclovir near term for women with recurrent herpes may decrease the need for abdominal deliveries. There are ongoing studies assessing the efficacy and safety of acyclovir given around the time of delivery for mother and child.

D. Herpes and HIV:

1. Genital ulcers increase the risk of HIV transmission and acquisition.
2. Frequent, persistent, severe, and atypical lesions in persons with HIV.
3. AIDS case definition if lesions persist >1 month in recurrent disease.
4. Benefit from increased doses of antiviral drugs has been demonstrated. High doses of valacyclovir were linked to hematologic disorders; however, this has not been seen using recommended doses.
5. Emergence of acyclovir-resistance in HIV.

VIII. References

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