

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 for clinical practice.
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 neonatal herpes and the role of HSV in HIV transmission.
7. Discuss the role of HSV screening and treatment in the prevention of neonatal herpes and HIV infection.
8. Recognize the role of HSV in individuals' sexual health

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I. Epidemiology

A. The virus:

1. A member of the human herpes viruses (herpesviridae), 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. HSV-1 may be increasing as a cause of first episode genital herpes in women, 16-21 year old persons and in certain population groups, particularly in Northern Europe.

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

D. It is estimated that at least one million new cases occur in the U.S. each year; over 80% of infections have not been diagnosed.

E. In the general U.S. population, 16% of persons ages 14 - 49 have HSV-2 antibodies. Among non-Hispanic whites, 9% of men and 16% of women are HSV-2 seropositive. HSV-2 seroprevalence is similar among Mexican Americans (8% of men and 13% of women) and higher among non-Hispanic blacks (29% of men and 48% of women). Seropositivity increases with age (26% among those aged 40-49 years) and reported number of lifetime sex partners (27% among those with 10 or more lifetime sex partners). In recent years, HSV-2 seroprevalence has been stable.

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; probably all HSV-2 seropositive individuals shed HSV-2 intermittently. Asymptomatic shedding occurs from 10 -27% of days.
- 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, and the presence of serum antibody to HSV-1 may be partially protective against acquisition of HSV-2 infection. HSV-1 seropositivity also partially protects against having a *symptomatic* infection. HSV-2 infection appears to be protective against acquisition of HSV-1.
- 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; thus fomite transmission is unlikely.
- N. Genital HSV-2 infection increases the subsequent risk of HIV-1 acquisition by 3 fold and facilitates the transmission of HIV infection.
- O. The projected U.S. rate of neonatal herpes is 33 per 100,000 live births; most (85%) of neonatal herpes cases are projected to occur in infants whose mothers are either HSV-seronegative or seropositive for HSV-1 only.

II. Pathogenesis

- A. After genital exposure and mucosal inoculation, the virus is transported along peripheral nerve axons to the nerve root ganglia.

- B. Once there, the virus enters a latent state where it can persist for the life of the host.
- 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 or viral shedding may occur in the absence of clinical signs or symptoms.
- 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-2 in an individual previously infected with HSV-1.
 - 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 HSV-2 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) Disease is usually mild and short in duration.
 - b) Antibody is present when symptoms appear, although the patient may not be aware of previous episodes.
 - c) Generally, there is no or little change in antibody titer in convalescence.
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 Characteristics

1. Primary (initial) infection without treatment: the characteristic picture is that of multiple lesions that are more severe, last longer, and have higher titers of virus than recurrent infections. Lesions start as papules and then evolve from

- vesicles to pustules, erosions and ulcers, after which they become crusted over and heal. The illness typically lasts 2-4 weeks.
- a) A primary infection is often associated with systemic symptoms, including fever, headache, malaise, myalgia (40% men, 70% women). Urinary retention occurs in 10% of women, particularly those with extensive vulvar involvement.
 - 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) Genital lesions are often numerous, bilateral, and painful. They 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 infection in women. 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 suggests HSV.
 - h) The exo-or endocervix may be involved.
2. Recurrent infection without treatment.
- a) About 70-90% of individuals with symptomatic HSV-2 and 20-50% of individuals with symptomatic genital HSV-1 infection will have a symptomatic recurrence in the first year.
 - b) Prodromal symptoms (localized tingling, irritation) occur in ~50% and begin 12-24 hours before lesions appear; sometimes prodromes occur without ensuing lesions ("false prodrome").
 - c) Duration is shorter than in primary infection: painful genital lesions last 4-6 days; the average duration of viral shedding is 4 days.
 - d) Lesions tend to be unilateral.

- e) Symptoms tend to be milder and less severe. Usually there are no systemic symptoms.
 - f) Rate of cervical virus shedding in women is 12-20%.
 - g) Recurrences average of 2-6 / year, but frequency is highly variable.
 - h) HSV-2 primary infection is much more prone to recur than HSV-1 primary infection.
 - j) HSV-2 will recur slightly more frequently and after shorter period of time in men than in women: in the first year of infection, men have a median of five recurrences per year compared with four among women.
 - k) Recurrences are more frequent if the primary episode lasts longer than 30 days.
3. Asymptomatic viral shedding:
- a) Most HSV-2 is transmitted during asymptomatic shedding.
 - b) Asymptomatic shedding has been documented in almost all HSV-2 seropositive persons studied. Rates are greatest in the first 3 months, and then decline.
 - c) Asymptomatic shedding is of briefer duration than shedding during clinical recurrences.
 - d) Rates of asymptomatic shedding are greater with HSV-2 than HSV-1.
 - e) Shedding (symptomatic and asymptomatic) as detected by PCR occurs on 10–27% of days and is lower among persons without a history of genital herpes.
 - f) Shedding is dramatically reduced, although not eradicated by acyclovir, valacyclovir or famciclovir suppression, especially among person with a history of genital herpes.
 - g) 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 rare, 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 is more commonly positive in primary infection (80-90%) as contrasted with recurrences (30%).
3. Time limitations: most cultures will be positive within 24-72 hours, but are generally held for 5-7 days.
4. HSV is stable in viral transport media for 48-72 hours at 4°C.
5. Culture allows for easy typing (type 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%), hence not recommended.
3. Nonspecific (cannot differentiate HSV from VZV).

D. Nucleic acid amplification testing (PCR and Strand Displacement Amplification (SDA)):

1. Highly specific and up to 4 times more sensitive than viral culture.
2. More expensive and not as widely available as culture.
3. Cleared only for use on specific types of body samples (e.g . PCR cleared for use on CSF and vesicle material, SDA cleared for use on anogenital lesions)

E. Serologic tests:

1. The older serological tests (CF, IFA, EIA) did not distinguish between HSV-1 and HSV-2 antibody and should not be used.
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 IG-based type-specific assays include the HerpeSelect 1 and 2 ELISA IgG; the HerpeSelect 1 and 2 Immunoblot IgG, and the Captia HSV-1 and 2 ELISA. Approved rapid (point of care) tests include the BioKit HSV-2 Rapid Test, the Sure-Vue HSV-2, and the HerpeSelect Express. The sensitivities of these tests for detection of HSV-2 antibody vary from 93-

100%. False-negative results may occur, especially early after infection. The specificities of these assays are 93-98%; 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. However, given the generally high prevalence of HSV-2 in the population and the even higher prevalence in high-risk populations (e.g., STD clinics), the positive predictive value of these tests is expected to be > 75%.

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 for planning pregnancy or pregnant couples.
- c) Screening in selected high-risk populations such as in STD clinics or HIV infected individuals. 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, universal screening for HSV-1 or HSV-2 infection in the general population is currently not recommended.
- d) IgM assays are not recommended except in the diagnostic evaluation of neonatal herpes.

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 and is therefore not recommended.
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 three times a day for 7-10 days or 200 mg five times a day for 7-10 days.
 - c) Famciclovir 250 mg three times a day for 7-10 days.
 - d) Valacyclovir 1 g twice a day for 7-10 days.
 - e) Treatment may be extended if healing is incomplete after 10 days of therapy.
 - f) Valacyclovir and famciclovir are likely to be effective for HSV proctitis or oral infection, but clinical experience is lacking.
 - g) Factors to weigh when considering treatment: severity of symptoms, immune status, pregnancy, history of complications, duration of symptoms, and cost.
3. Intravenous medication:
 - a) For use in severe disease or complications that necessitate hospitalization (e.g. disseminated infection, pneumonitis, or hepatitis) or CNS complications (e.g. meningoencephalitis).
 - b) Dose: acyclovir 5-10 mg/kg every 8 hours for 2-7 days or until clinical improvement is observed. After clinical improvement, oral administration of acyclovir, valacyclovir or famciclovir is recommended for a total of 10 days.
4. Recommended oral regimens for treatment of episodic recurrent infection:
 - a) Acyclovir 400 mg 3 times a day for 5 days, or 800 mg twice a day for 5 days, or 800 mg three times a day for 2 days
 - b) Famciclovir 125 mg twice a day for 5 days, or 1 g twice daily for 1 day, or 500 mg once followed by 250 mg twice daily for 2 days

- c) Valacyclovir 500 mg twice a day for 3 days or valacyclovir 1 g once a day for 5 days.
 - d) 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 within 1 day of lesion onset or during the prodrome that precedes some outbreaks.
5. Recommended oral regimens for 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 70-80%.
 - c) Acyclovir has been used safely for up to 6 years; valacyclovir and famciclovir for 1 year.
 - d) Acyclovir 400 mg twice a day.
 - e) Famciclovir 250 mg twice a day. Appears somewhat less effective for suppression of viral shedding.
 - f) Valacyclovir 500 mg once daily or 1 g once daily (valacyclovir 500 mg once a day appears less effective than other valacyclovir or acyclovir dosing regimens in patients who have very frequent recurrences (i.e. >10 episodes per year).
 - g) Suppressive therapy should be continued for 1 year; at that point discontinuation should be discussed 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. Recommended oral regimens for episodic and suppressive therapy in *HIV infection*:
- 1. Episodic: acyclovir 400 mg three times a day for 5-10 days, or famciclovir 500 mg twice daily for 5-10 days, or valacyclovir 1 g twice daily for 5-10 days.
 - 2. Suppressive: acyclovir 400-800 mg twice a day or three times a day; or famciclovir 500 mg twice a day; or valacyclovir 500 mg twice a day.
 - 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 40 mg/kg every 8 hours until clinical resolution is attained, is considered the therapy of choice. Intravenous cidofovir 5 mg/kg once weekly might also be effective. Imiquimod is a topical alternative, as is topical cidofovir gel 1%, which is not commercially available and must be compounded at a pharmacy (topical preparations should be applied to the lesions once daily for 5 consecutive days).
2. To suppress recurrent episodes of acyclovir-resistant HSV in immunosuppressed patients, once or twice weekly Foscarnet injections may be necessary.

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 topical analgesics are of unproven benefit, but some patients report relief.
3. Sitz baths.

VI. Prevention

Diagnosis of HSV can be upsetting to patients. Common concerns regarding genital herpes include severity of initial clinical manifestations, recurrent episodes, impact on sexual relationships, transmission to partners, and ability to bear healthy children. Misconceptions such as “HSV causes cancer” should be dispelled. It is important for clinicians to be nonjudgmental, to normalize (e.g. “Lots of my patients feel this way”); and to show empathy (e.g. “I can see you have a lot on your mind”) when treating HSV. Clinicians should work to reassure patients that they can still do many things to stay healthy and maintain sexual health after an HSV diagnosis. Clinicians can do this by framing discussions positively in terms of “staying healthy” and maintaining sexual health.

A. Patient counseling and education:

Patients should be counseled and educated on ways to stay sexually healthy following an HSV diagnosis. Although initial counseling can be provided at the first visit, many patients benefit from learning about chronic aspects of HSV infection after the acute illness subsides. Patients may also find other reputable sources of information from the internet useful and clinicians may be able to help facilitate this.

1. Nature of the infection
 - a) The natural history of the disease should be discussed with the patient with emphasis on maintaining sexual health following HSV infection. Patients should understand the potential for recurrent episodes, asymptomatic viral shedding, and attendant risks of sexual transmission.
 - b) One specific way to maintain sexual health is to assure patients having a first episode of genital herpes that suppressive antiviral therapy is available and effective in preventing symptomatic recurrent episodes and that episodic therapy is useful in shortening the duration of recurrent episodes.
 - c) Patients should be informed that frequency of outbreaks generally decreases with increasing duration of infection.
 - d) Patients should be educated about prodromal symptoms and when/how to take medication.
 - e) 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 clinical manifestations of genital herpes to help them better identify these over time.
2. Transmission issues: counseling for the patient and regular sexual contacts to maintain sexual health:
 - a) The history of disease should be discussed with emphasis on maintaining sexual health following HSV infection. Patients should understand the potential for recurrent episodes, asymptomatic viral shedding, and attendant risks of sexual transmission.
 - b) 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. Clinicians can help patients explore ways to do this.

- 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) Patients should be advised to abstain from sexual activity, and explore other non-sexual forms of intimacy with uninfected partners when lesions or prodromal symptoms are present.
 - e) Risk for HSV-2 sexual transmission can be decreased by daily use of valacyclovir by the infected person. Episodic therapy does not reduce the risk of transmission and its use should be discouraged for this purpose among persons whose partners might be at risk for HSV2 acquisition.
 - f) 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.
 - g) 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., oral sex with a partner with oral herpes, and vaginal intercourse with a partner with genital HSV-1 infection).
 - h) When exposed to HIV, HSV-2 seropositive persons are at increased risk for HIV acquisition. However, suppressive antiviral therapy does not reduce the increased risk for HIV acquisition associated with HSV-2 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 and 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:

- d) Efficacy of determining type-specific HSV serostatus in high-risk groups with or without subsequent antiviral suppression has not been shown to be cost-effective in terms of preventing further cases and sequelae.
- e) Investing 15 minutes in education and counseling at the initial patient visit is associated with patient satisfaction with management of physical symptoms.
- f) Evidence shows that patients want their clinicians to discuss sexual health issues and that patients often expect their clinicians will initiate these discussions.

B. Partner management:

The potential for HSV to affect relationships should be acknowledged. Providers should discuss ways the sexual partners of patients with HSV can stay sexually healthy when one or both partners have HSV.

1. Sex partners can benefit from evaluation and counseling. Symptomatic sex partners should be evaluated and treated in the same manner as patients who have genital lesions.
2. Asymptomatic sex partners of patients who have genital herpes should be advised that they might be infected even if they have no symptoms, and should be asked about their histories of genital lesions, counseled to recognize symptoms of herpes, and offered type-specific serologic testing for HSV infection.

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.
3. LGV should be considered in the differential diagnosis, especially among MSM.

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. Nonetheless, men with symptomatic genital herpes who are also diagnosed with non-gonococcal urethritis should receive standard recommended treatment for NGU (i.e., azithromycin or doxycycline).
2. HSV has been isolated from ~5% of women with the dysuria-frequency syndrome.

C. Herpes in pregnancy:

1. Most women with HSV have healthy pregnancies. However, in vaginal delivery, risk of transmission is high (30-50%) among women who acquire genital herpes near the time of delivery, and low (<1%) among women with histories of recurrent herpes at term or who acquire genital herpes during the first half of pregnancy. Because recurrent genital herpes is much more common than initial HSV infection during pregnancy, the proportion of neonatal HSV infections acquired from mothers with recurrent herpes is substantial.
2. Risk factors for HSV transmission to the infant include: new infection, primary infection, lack of type-specific antibodies, and scalp electrodes.
3. Women with active recurrent genital herpes should be offered suppressive viral therapy at or beyond 36 weeks of gestation, because this therapy has been shown to reduce recurrence at the time of delivery and cesarean delivery for genital HSV.
4. Abdominal delivery (cesarean section) is recommended when prodromal symptoms or active lesions occur at the onset of labor, regardless of whether this is a primary or recurrent outbreak.
5. Data regarding interventions to reduce vertical transmission in the specific setting of primary herpes are limited. A meta-analysis of 5 studies found a

significant reduction in clinical recurrences at delivery when women were given acyclovir from 36 weeks of gestation to delivery with an associated decrease in cesarean sections related to clinical herpes recurrences.

6. Cesarean delivery is not recommended for women with a history of HSV infection but no active genital disease during labor.
7. Routine antepartum genital HSV cultures in asymptomatic patients with recurrent disease are not recommended.
8. Routine HSV screening of pregnant women is currently not recommended but can be offered as part of prenatal care
9. Prevention must center on avoiding acquisition of HSV in late pregnancy. To avoid acquisition, women without known genital herpes should be counseled to abstain from intercourse during third trimester with partners known or suspected of having genital herpes, and women without known orolabial herpes should be advised to abstain from receptive oral sex during third trimester with partners known or suspected to have orolabial herpes. The new type-specific serologies may be of use in determining risk status and management of HSV in pregnancy in particular for women with a clinical diagnosis of genital herpes, a history of atypical recurrent genital lesions, or a past or present partner with a history of genital herpes.

D. Herpes and HIV.

1. Genital ulcers increase the risk of HIV transmission and acquisition.
2. HIV-infected persons may have herpetic lesions that are more frequent, persistent, severe, and atypical.
3. Herpes lesions persisting >1 month in recurrent herpes among HIV-infected persons is an AIDS-defining illness.
4. Benefit from increased doses of antiviral drugs has been demonstrated. However, high doses of valacyclovir (8 grams per day) have been linked to hematologic disorders.

5. Acyclovir-resistant herpes is common among persons with HIV infection. If lesions persist or recur in a patient receiving antiviral treatment, HSV resistance should be suspected and a viral isolate should be obtained for sensitivity testing.
6. Although anti-herpetic treatment has been demonstrated to decrease HIV viral load among persons with HIV infection, anti-herpetic treatment has not been shown to reduce HIV transmission and acquisition.
7. HIV infected individuals should be screened for HSV-2 infection.

VIII. References

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