



Ready-to-Use

STD Curriculum for Clinical Educators

Genital Herpes Simplex Virus (HSV) Module

Target Audience - Faculty in clinical education programs, including those programs that train advanced practice nurses, physician assistants, and physicians

Contents - The following resources are provided in this module:

- **Faculty Notes** (Microsoft Word and Adobe Acrobat formats) - Includes notes that correspond to the slide presentation, a case study with discussion points, and test questions with answers
- **Slide Presentation** (Microsoft PowerPoint and Adobe Acrobat formats)
- **Student Handouts**
 - **Case Study** (Microsoft Word format)
 - **Test Questions** (Microsoft Word format)
 - **Slides Handout** (Adobe Acrobat format)
 - **Resources** (Microsoft Word format)

Suggested Time Allowance - The approximate time needed to present this module is 60-90 minutes.

These materials were developed by the Training and Health Communication Branch, Division of STD Prevention, CDC. They are based on the curriculum developed by the National Network of STD/HIV Prevention Training Centers (NNPTC) which includes recommendations from the 2002 CDC STD Treatment Guidelines.

Information on the NNPTC can be accessed at:
<http://www.stdhivpreventiontraining.org>

The 2002 CDC STD Treatment Guidelines can be accessed or ordered online at:
<http://www.cdc.gov/std/treatment/default.htm>



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Genital Herpes Simplex Virus (HSV)

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Learning Objectives

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

1. Describe the epidemiology of genital HSV infection in the U.S.
2. Describe the pathogenesis of genital HSV.
3. Discuss the clinical manifestations of genital HSV infection.
4. Identify the common laboratory tests used in the diagnosis of genital HSV infection.
5. Describe patient management for genital HSV infection.
6. List public health measures for the prevention of genital HSV infection.
7. Summarize appropriate prevention counseling messages for genital HSV infection.

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Course Outline

- I. Epidemiology: Disease in the U.S.
- II. Pathogenesis
- III. Clinical manifestations
- IV. Diagnosis
- V. Patient management
- VI. Prevention

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I. Epidemiology

[Slides 5-7]

- A. Incidence and prevalence
 1. Genital herpes is a recurrent, life-long viral infection.
 2. Two serotypes of herpes simplex virus (HSV) have been identified: HSV-1 and HSV-2.
 3. The majority of genital and perirectal herpetic outbreaks in the U.S. are caused by HSV-2, although up to 30% of first episodes are due to HSV-1.
 4. It is estimated that at least 1 million new cases occur each year.
 5. 50% or more of new cases are asymptomatic or unrecognized.
 6. In the general U.S. population, 22% of adults over age 12 have HSV-2 antibodies.
 7. HSV-2 antibodies are not routinely detected until puberty, and HSV-2 seroprevalence rates increase with age up to 40 years then level off.

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- B. Transmission
 1. HSV-2 is transmitted sexually (genital to genital, oral to genital, or genital to oral) and perinatally (mother to child). HSV-1 is usually transmitted via a non-sexual route.

2. Most sexual transmission occurs while the source contact case is asymptomatic.
3. 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.
4. Efficiency of sexual transmission is greater from men to women than from women to men.
5. 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.
6. Likelihood of transmission (frequency of occurrences and asymptomatic viral shedding) to others declines with increased duration of infection.
7. Incubation period after acquisition is 2-12 days (average is 4 days).
8. Drying and soap and water readily inactivate HSV; therefore, fomite transmission is unlikely.
9. Genital HSV-2 infection facilitates both acquisition and transmission of HIV infection.

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II. Pathogenesis

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A. Virology

1. Members of the human herpes viruses (herpetoviridae), which include: HSV-1, HSV-2, VZV, EBV, CMV, HHV-6, HHV-7, HHV-8.
2. HSV-1 and HSV-2 are double-stranded DNA viruses surrounded by an envelope of lipid glycoprotein.
3. 50% DNA homology exists 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 resulting in recurrent disease. Re-infection can occasionally occur despite immunity.

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B. Pathogenesis

1. Transmission of HSV usually occurs through close contact with a person who is shedding virus at a peripheral site, mucosal surface, or in genital or oral secretions.
 - a) HSV penetrates susceptible mucosal surfaces or abraded cracks in the skin.
 - b) After mucosal inoculation (in genital infection), the virus is transported along peripheral nerve axons to the nerve cell bodies' sacral ganglia.
 - c) Virus remains latent indefinitely in the paraspinal ganglia.
 - d) Reactivation, precipitated by multiple known (e.g., trauma, fever, UVL, stress, etc.) and unknown factors, induces viral replication.

- e) 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.
- 2. 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.
- 3. 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.

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III. Clinical Manifestations

[Slides 15-17]

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 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) 25% 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.
 - c) Disease is usually mild and short in duration.
- 3. Asymptomatic infection
 - a) Serum antibody is present
 - b) No known history of clinical outbreaks
 - c) Up to two-thirds of patients with identified asymptomatic HSV-2 infection actually have unrecognized symptomatic infection.
 - d) Patients should be informed about clinical signs and symptoms of genital herpes, as this may help them recognize symptomatic infection.

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	-	+/-	+

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B. Clinical manifestations

1. Primary (initial) infection without treatment: characterized by the occurrence of numerous bilateral painful genital lesions. These lesions are more severe, last longer, and have higher titers of virus than recurrent infections.
 - a) Lesion progression: papules → vesicles → pustules → ulcers → crusts → healed
 - b) Illness lasts 2-4 weeks.
 - c) Often associated with systemic symptoms, including fever, headache, malaise, myalgia; urinary retention in women.
 - d) Systemic symptoms peak within 3-4 days of onset of lesions and gradually recede over the next 3-4 days.
 - e) Local symptoms are predominantly pain, itching, dysuria, vaginal or urethral discharge, and tender inguinal adenopathy (80%).
 - f) 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.
 - g) Median duration of viral shedding (from the onset of lesions to the last positive culture) is approximately 12 days, and correlates well with the mean time from the onset of vesicles to crusting.
 - h) 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.
 - i) Primary HSV cervicitis occurs in approximately 90% of primary HSV-2 infection and about 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. The exo-or endocervix may be involved. Herpes proctitis may be characterized by pain, discharge, tenesmus, constipation with or without symptoms of autonomic dysfunction and severe ulceration on anoscopy.

j) Urinary involvement

- 1) Men with first-episode HSV have a positive urethral culture in 33% of cases. 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 approximately 5% of women with the dysuria-frequency syndrome.

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Image: Herpes: Primary complex

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Image: Herpes: Genitalis multiple ulcer

[Slide 22]

Image: Herpes: Genitalis external-labia minor

[Slide 23]

Image; Herpes: Genitalis clinical periurethral lesions on vestibule

[Slide 24]

Image: Herpes: Cervicitis

[Slide 25]

Image: Herpes on the buttock

[Slide 26]

Image: Herpes: Possible oralis soft palate

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2. Recurrent infection without treatment
 - a) Illness lasts 5-10 days
 - b) Prodromal symptoms (localized tingling, irritation) in approximately 50% begin 12-24 hours before lesions and sometimes without lesions ("false prodrome").
 - c) Duration is shorter than in primary infection: painful genital lesions last 4-6 days; 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) Average of 2-6 recurrences/year, but highly variable.

- h) HSV-2 primary infection is much more prone to recur than HSV-1 primary infection.
- i) HSV-2 will recur slightly more frequently and after a shorter period of time in men than in women; median 5 recurrences per year compared with 4 in the first year of infection.
- j) Recurrences are more frequent if the primary episode is prolonged > 30 days.

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- 3. Asymptomatic viral shedding
 - a) Asymptomatic shedding as detected by PCR is present on 28% of days (range 0 to 77%).
 - b) Rates of asymptomatic shedding are greater with HSV-2 than with HSV-1.
 - c) Asymptomatic shedding has been documented in almost all HSV-2 seropositive persons studied.
 - d) Most HSV-2 is transmitted during asymptomatic shedding.
 - e) Shedding rates are greatest in the first 3 months after infection.
 - f) Asymptomatic shedding occurs less frequently in women with established HSV-2 infection (mean--4% of days). In those with newly acquired infections (<2 years), asymptomatic shedding occurs in up to 5%-10% of days.
 - g) Asymptomatic shedding is of briefer duration than during clinical recurrences.
 - h) Presence of serum antibody of HSV-1 seems to decrease rates of asymptomatic shedding with HSV-2.
 - i) Acyclovir chemosuppression dramatically reduces, but does not eradicate shedding.
 - 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) Most common sites of asymptomatic shedding are the vulva and perianal areas in women and penile skin and perianal area in men.

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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 versus 11% of men with primary HSV-2 infection)
 - d) May be severe, requiring hospitalization 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 complications (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)

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IV. Diagnosis

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A. Diagnosis

1. Clinical diagnosis is insensitive and nonspecific.
2. The typical painful multiple vesicular or ulcerative lesions are absent in many infected persons. Up to 30% of first-episode cases are caused by HSV-1, but recurrences are much less frequent for genital HSV-1 infection than genital HSV-2 infection, therefore HSV serotype influences prognosis and counseling.
3. Clinical diagnosis should be confirmed by lab testing; there are 2 main types of lab tests used for confirmatory diagnosis:
 - a) Virologic tests
 - b) Type-specific serologic tests

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B. Virologic tests

1. Viral culture (gold standard)
 - a) Isolation of HSV in cell culture is the preferred test for patients with genital ulcers or other mucocutaneous lesions.
 - b) Sensitivity of culture declines rapidly as lesions begin to heal, usually within a few days of onset.
 - c) Highly specific (>99%) and sensitive but not as sensitive as PCR.
 - d) 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%).
 - e) Time limitations: most cultures will be positive within 24-72 hours, but are generally held for 5-7 days.
 - f) Stable in viral transport media for 48-72 hours at 4°C.
 - g) Allows for easiest typing (HSV-1 vs. HSV-2).
2. Antigen detection (DFA or EIA)
 - a) Some HSV antigen tests, unlike culture and the direct fluorescent antibody test, do not distinguish HSV-1 from HSV-2.
 - b) Fairly sensitive (>85%) in symptomatic shedders

- c) Rapid (2-12 hours)
- d) Highly specific; can differentiate HSV-1 from HSV-2 or VZV using monoclonal antibodies, but false positives can occur.
- e) May be better than culture for healing lesions
- 3. Cytology (Tzanck or Pap)
 - a) Cytologic detection of cellular changes of herpes virus infection is insensitive (50%) and nonspecific (cannot differentiate HSV from VZV) and should not be relied on for HSV diagnosis.
 - b) Identifies typical HSV-infected cells (multi-nucleated giant cells and eosinophilic inclusion bodies) in exfoliated cells or biopsies.
 - c) Cytologic tests include Tzanck preparation for genital lesions and cervical Pap smears.
- 4. PCR assay is the preferred test for detecting HSV in spinal fluid. PCR is highly sensitive and specific, but its role in diagnosis of genital ulcer disease has not been well-defined.
- 5. Comparison of virologic tests:

	Viral culture	Antigen detection (DFA or EIA)	Cytology (Tzanck or Pap)	PCR
Sensitivity	80%-90% (primary episode)	>85% (in symptomatic shedders)	50%	
Specificity	99%		Non-specific	
Test notes	Positive in 80%-90% of primary infections and 30% of recurrent infections; allows for easiest typing; most are positive in 1-3 days, but held 5-7 days	May be better than culture for healing lesions; rapid (2-12 hours)	Identifies typical HSV-infected cells in exfoliated cells or biopsies	Clinical significance of positive result being established

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C. Serologic tests

1. Type-specific and nonspecific antibodies to HSV develop during the first several weeks following infection and persist indefinitely.
2. Presence of HSV-2 antibody indicates anogenital infection.

3. Presence of HSV-1 does not distinguish anogenital from orolabial infection.
4. The older serological tests (CF, IFA, EIA) did not distinguish between HSV-1 and HSV-2 antibody.
5. New serological tests using HSV type-specific antigens glycoprotein G1 (HSV-1) and glycoprotein G2 (HSV-2) and EIA and Western blotting (WB) methods have been developed and are now commercially available for type-specific testing. Currently the FDA-approved glycoprotein G (gG)-based type-specific assays include laboratory-based assays manufactured by Focus Technology, Inc: HerpeSelect™ ELISA IgG and HerpeSelect™ Immunoblot. 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 > 96%; false-positive results can occur, especially in patients with low likelihood of HSV infection. Therefore, repeat testing or a confirmatory test may be indicated in some settings.
6. Uses of type-specific serologic tests:
 - a) To confirm clinical diagnosis in cases of recurrent or healing lesions or atypical genitourinary symptoms where false-negative HSV cultures are more common
 - b) To diagnose unrecognized infection
 - c) To manage sex partners of persons with genital herpes and to counsel couples in which one of the pair has genital herpes and the other does not know or is unsure (may be valuable in planning pregnancy or for expectant couples)
 - d) To screen in selected high-risk populations such as STD clinic patients. Cost-benefit analyses have not been performed comparing the costs of the tests vs. the savings resulting from preventing further cases.
7. 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.

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D. Special diagnostic considerations

1. Establish the etiology of atypical genital ulcer(s) to include mixed infections (e.g., syphilis and chancroid), 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.

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V. Patient Management

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A. Principles of management of genital herpes

1. Systemic antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management.

- a) Partially controls symptoms and signs of herpes episodes when used to treat first clinical episodes and recurrent episodes or when used as daily suppressive therapy.
- b) Does not eradicate latent virus and does not affect risk, frequency, or severity of recurrences after drug is discontinued.
- 2. Counseling is integral to clinical management and should include natural history, sexual and perinatal transmission, and methods to reduce transmission.

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B. Antiviral therapy for HSV

- 1. HSV systemic antiviral chemotherapy includes three oral medications:
 - a) Acyclovir (ACV)
 - b) Valacyclovir (Valine ester of acyclovir)--high oral bioavailability
 - c) Famciclovir (Penciclovir prodrug)--high oral bioavailability
- 2. Topical antiviral treatment is of minimal clinical benefit and is not recommended.

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C. Management of first clinical episode of genital herpes

- 1. Many patients with first episode herpes present with mild clinical manifestations but later develop severe or prolonged symptoms. Therefore, most patients with initial genital herpes should receive antiviral therapy.
- 2. Antiviral therapy has dramatic effect in initial HSV infection, especially if symptoms <7 days and no history of oral HSV.

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- 3. CDC-recommended regimens for the treatment of first clinical episode
 - a) Acyclovir 400 mg orally 3 times a day for 7-10 days until complete crusting has occurred, or
 - b) Acyclovir 200 mg orally 5 times a day for 7-10 days, or
 - c) Famciclovir 250 mg orally 3 times a day for 7-10 days, or
 - d) Valacyclovir 1 g orally twice a day for 7-10 days.
- 4. Higher dosages of acyclovir (e.g., 400 mg orally 5 times a day) were used in treatment studies of first-episode herpes proctitis and first-episode oral infection. However, no comparative studies have been conducted, and whether these forms of HSV infection require higher doses of antiviral drugs than used for genital herpes is unknown. Valacyclovir and famciclovir probably are also effective for acute HSV proctitis or oral infection, but clinical experience is lacking.
- 5. Treatment may be extended if healing is incomplete after 10 days of therapy.
- 6. Factors to weigh when considering treatment: severity of symptoms, immune status, pregnancy, history of complications, and cost.

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D. Recurrent episodes of genital herpes

1. Most patients with symptomatic primary genital HSV-2 infection experience recurrent outbreaks.
2. Recurrences are less frequent after initial HSV-1 infection.
3. Antiviral therapy for recurrent genital herpes can be administered either episodically, to ameliorate or shorten the duration of lesions, or continuously as suppressive therapy, to reduce the frequency of occurrences.
4. Treatment options should be discussed with ALL patients.

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5. Episodic therapy
 - a) Successful episodic treatment requires initiation of therapy within 1 day of lesion onset.
 - b) Clinicians should provide the patient with a supply of drug or a prescription and instructions to self-initiate treatment immediately when symptoms begin.

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6. CDC-recommended regimens for episodic therapy for recurrent infection
 - a) Acyclovir 400 mg orally 3 times a day for 5 days, or
 - b) Acyclovir 200 mg orally 5 times a day for 5 days, or
 - c) Acyclovir 800 mg orally twice a day for 5 days; or
 - d) Famciclovir 125 mg orally twice a day for 5 days, or
 - e) Valacyclovir 500 mg orally twice a day for 3-5 days, or
 - f) Valacyclovir 1 g orally once a day for 5 days.
7. 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.

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8. Suppressive therapy
 - a) Suppressive therapy reduces the frequency of genital herpes recurrences by 70%-80% among patients who have frequent recurrences (> 6 recurrences per year), and many patients report no symptomatic outbreaks.
 - b) Treatment probably is also effective in patients with less frequent recurrences, although definitive data are lacking.
 - c) Quality of life often is improved in patients with frequent recurrences who receive suppressive therapy compared with episodic therapy.
 - d) Suppressive antiviral therapy reduces but does not eliminate subclinical viral shedding and decreases transmission 48%-75% in the susceptible partner in discordant couple studies.

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9. CDC-recommended regimens for suppressive therapy for recurrent infection
 - a) Acyclovir 400 mg orally twice a day, or
 - b) Famciclovir 250 mg orally twice a day, or

- c) Valacyclovir 500 mg orally once a day, or
 - d) Valacyclovir 1 g orally once a day.
10. Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens in patients who have very frequent recurrences (i.e., >10 episodes per year).
 11. Ease of administration and cost are important considerations for prolonged treatment.
 12. The frequency of recurrent outbreaks diminishes over time in many patients, and the patient's psychological adjustment to the disease may change.
 - a) Periodically during suppressive treatment (e.g., once a year), discontinuation of therapy should be discussed with the patient to reassess the need for continued suppressive therapy.
 - b) Patients should be warned that they might have rebound outbreaks when suppression is discontinued; suppression does not eliminate ganglionic latency.

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E. Severe disease

1. IV acyclovir should be provided for patients with severe disease or complications requiring hospitalization such as disseminated infection, pneumonitis, hepatitis, or complications of the central nervous system (e.g., meningitis or encephalitis).
2. CDC-recommended regimen
 - a) Acyclovir 5-10 mg/kg IV every 8 hours for 2-7 days or until clinical improvement, followed by oral antiviral therapy to complete at least 10 days total therapy.
3. Allergic and other adverse reactions to acyclovir, valacyclovir, and famciclovir are rare.
4. Desensitization to acyclovir is described in Henry RE, et al. Successful oral acyclovir desensitization. *Ann Allergy* 1993; 70:386-8.

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F. Herpes and HIV

1. Immunocompromised patients may have prolonged or severe episodes of genital, perianal, or oral herpes.
2. Herpes lesions are common in HIV-infected patients and may be persistent, severe, painful, and atypical.
3. Genital ulcers increase the risk of HIV transmission and acquisition.
4. AIDS case definition applies if lesions persist >1 month in recurrent disease.

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5. CDC-recommended regimens for episodic therapy for HIV-infected persons
 - a) Acyclovir 400 mg orally 3 times a day for 5-10 days, or
 - b) Acyclovir 200 mg orally 5 times a day for 5-10 days, or
 - c) Famciclovir 500 mg orally twice a day for 5-10 days, or
 - d) Valacyclovir 1 g twice a day for 5-10 days.

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6. CDC-recommended regimens for suppressive therapy for HIV-infected persons
 - a) Acyclovir 400-800 mg orally twice to 3 times a day, or
 - b) Famciclovir 500 mg orally twice a day, or
 - c) Valacyclovir 500 mg orally twice a day.
7. In doses recommended for treatment of genital herpes, acyclovir, valacyclovir, and famciclovir are safe for use in immunocompromised patients. For severe cases, initiating therapy with acyclovir 5-10 mg/kg IV every 8 hours may be necessary.
8. If lesions persist or recur in a patient receiving antiviral treatment, HSV resistance should be suspected and a viral isolate obtained for sensitivity testing. Such patients should be managed in consultation with a specialist, and alternative therapy should be administered. All acyclovir-resistant strains are resistant to valacyclovir and most are resistant to famciclovir. (Refer to the CDC 2002 STD Treatment Guidelines for treatment alternatives <http://www.cdc.gov/STD/treatment/>).

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G. Herpes in pregnancy

1. Risk for transmission to neonate from infected mother is high (30%-50%) in women who acquire genital herpes near time of deliver and low (<1%) in women with histories of recurrent herpes at term or who acquire genital HSV during the first half of pregnancy.
2. Prevention of neonatal herpes depends on avoiding acquisition of HSV during late pregnancy and avoiding exposure of infant to herpetic lesions during delivery. Type-specific serologic tests may be useful in determining risk status and management of HSV in pregnancy.
3. Counsel all women without known genital herpes to avoid intercourse during 3rd trimester with partners known or suspected of having genital herpes.
4. Counsel all women without known orolabial herpes to avoid cunnilingus during 3rd trimester with partners known or suspected of having orolabial herpes.
5. Ask all pregnant women whether they have a history of genital herpes.
6. At onset of labor:
 - a) Question all women about symptoms of genital herpes, including prodrome.
 - b) Examine all women for herpetic lesions.
7. Women without symptoms or signs of genital herpes or its prodrome can deliver vaginally.
8. Most specialists recommend that women with recurrent genital herpetic lesions at onset of labor deliver by cesarean section to prevent neonatal herpes. However, abdominal delivery does not completely eliminate the risk for HSV transmission to the infant.

9. Risk factors for HSV transmission to the infant include: new infection, primary infection, lack of type-specific antibodies, and use of scalp electrodes.
 10. The results of viral cultures during pregnancy in women with or without visible herpetic lesions do not predict viral shedding at the time of delivery, and therefore routine viral cultures of pregnant women with recurrent genital herpes are not recommended.
 11. 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 cesarean 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.
 12. Acyclovir may be administered orally to pregnant women with first episode genital herpes or severe recurrent herpes and should be administered IV to pregnant women with severe HSV infection.
 13. Safety of systemic acyclovir, valacyclovir, and famciclovir therapy in pregnant women has not been established, although available data do not indicate increased risk for major birth defects compared with the general population in women treated with acyclovir during the first trimester. There are ongoing studies assessing the efficacy and safety of acyclovir given around the time of delivery for mother and child.
- H. Therapy of complicated HSV infection
1. The therapy of choice in acyclovir resistant HSV infections is intravenous sodium phosphonoformate (Foscarnet).
 2. Foscarnet injections once or twice weekly may be necessary to suppress recurrent episodes of Acyclovir resistant HSV in immunosuppressed patients.
 3. Cidofovir gel is currently under investigation and is not available for use at this time.
- I. 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--of unproven benefit, but some patients report relief.
 3. Sitz baths

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VI. Patient Counseling and Education

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- A. Counseling
1. Counseling has two main goals:
 - a) To help patients cope with the infection, and
 - b) To prevent sexual and perinatal transmission.
 2. Psychological impact of infection is often substantial.
 3. HSV-infected persons may express anxiety about genital herpes that does not reflect the actual clinical severity of their disease.

4. The misconception that HSV causes cancer should be dispelled, because HSV-2 is not a primary etiologic agent in cervical cancer.
5. Common concerns about genital herpes include the severity of initial clinical manifestations, recurrent episodes, sexual relationships and transmission to sex partners, and ability to bear healthy children.
6. Although initial counseling can be provided at first visit, many patients benefit from learning about the chronic aspects of the disease after the acute illness subsides.
7. Numerous resources are available to assist patients and clinicians in counseling (see the Resources list at the end of this module for more information).

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- B. Patient counseling and education should include:
1. Nature of the infection
 2. Transmission
 3. Treatment issues
 4. Risk reduction strategies
 5. An emphasis on the potential for recurrent episodes, asymptomatic viral shedding, and sexual transmission

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- C. Nature of the infection
1. Sexual transmission of HSV can occur during asymptomatic periods
 2. The frequency of outbreaks generally decreases with increasing duration of infection
 3. Stressful events may trigger recurrences
 4. Prodromal symptoms may precede outbreaks

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- D. Transmission
1. HSV can be transmitted when lesions are not present and most cases are transmitted during asymptomatic periods.
 2. Abstain from sexual activity with uninfected partners when lesions or prodromal symptoms are present.
 3. Inform current sex partners about diagnosis of genital herpes.
 4. Inform future partners before initiating a sexual relationship.

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- E. Treatment options
1. Effectiveness of suppressive and episodic therapy in preventing or shortening the duration of recurrent episodes
 2. When and how to take antiretroviral medications
 3. Recognition of prodromal symptoms
 4. Strategies for relief of painful urination such as urinating in a tub and the use of topical analgesics

[Slide 63]

F. Risk reduction strategies

1. Assess client's behavior-change potential.
2. Discuss prevention strategies (abstinence, mutual monogamy with an uninfected partner, condoms, limiting the number of sex partners, etc.).
3. Inform the patient that genital ulcer diseases can occur in male or female genital areas that are covered or protected by a latex condom, as well as in areas that are not covered.
4. 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.
5. Work with the patient to develop individualized risk-reduction plans.
6. Risk of neonatal infection should be explained to all patients, including men.
7. Advise pregnant women and women of child-bearing age to inform their prenatal and neonatal care providers that they have genital herpes.

[Slide 64]

G. Counseling for asymptomatic persons

1. Give asymptomatic persons diagnosed with HSV-2 infection by type-specific serologic testing the same counseling messages as persons with symptomatic infection.
2. Teach about the common manifestations of genital herpes, as many will become aware of them with time.
3. Antiviral therapy is not recommended for persons without clinical manifestations of infection.
4. Type-specific serological testing of asymptomatic partners can determine whether risk of HSV acquisition exists.

[Slide 65]

VII. Partner Management

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

CASE STUDY

[Slide 67]

Roberta Patterson is a 26-year-old woman who presents for her first prenatal visit. She is concerned for her baby because of her husband Franklin's history of genital herpes. She states that she is 6 weeks pregnant.

History

- Roberta has never had symptoms of vaginal or oral herpes.
- She was diagnosed and treated for chlamydia seven years ago (age 19); no other STD diagnoses reported.
- Her 26-year-old husband had his first episode of genital herpes during his last year of high school; no other STD diagnoses reported.
- Her husband (and sex partner for the last 16 months) has not had HSV lesions visible since she's been sexually active with him, and reports having had no prodromal symptoms or symptoms of active disease.
- She has had no sex partners, other than her husband, for the last 16 months.

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Physical Exam

- Vital signs: blood pressure 112/68, pulse 58, respiration 13, temperature 38.5° C
- Cooperative, good historian
- Chest, heart, musculoskeletal, and abdominal exams within normal limits
- Uterus consistent with a 6-week pregnancy
- Normal vaginal exam without signs of lesions or discharge
- No lymphadenopathy

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1. Which HSV general education messages should be discussed with Roberta?

Correct responses include the following:

- Genital herpes is a recurrent, life-long viral infection.
- HSV-2 causes the majority of genital herpes cases in the U.S.
- At least 50 million people in the U.S. have genital HSV infection.
- Most persons infected with HSV-2 are undiagnosed.
- 50% or more of new cases are asymptomatic or unrecognized.
- Most sexual transmission occurs while the source case is asymptomatic.
- Up to 90% of persons seropositive for HSV-2 antibody have no clinical history of anogenital herpes outbreaks.

2. Given that Roberta's husband Franklin has a history of genital herpes, would it be appropriate to test Roberta for genital herpes using a type-specific serologic test?

Yes, it would be appropriate to use a type-specific serologic test to test Roberta for genital herpes, given that she is pregnant and her husband has a history of genital

herpes. Some specialists believe type-specific serologic tests are useful to identify pregnant women at risk for HSV infection and to guide counseling with regard to the risk of acquiring genital herpes during pregnancy. Such testing and counseling may be especially important when a woman's sex partner has HSV infection.

3. What other STD screening should be considered for Roberta?

Because of the potential for neonatal infection, CDC recommends screening all pregnant women for syphilis, chlamydia, gonorrhea, and HIV.

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Roberta's Laboratory Results

- HSV gG-based type-specific serologies: HSV-1 negative; HSV-2 positive
- DNA probe for *Chlamydia trachomatis*: negative
- Culture for *Neisseria gonorrhoeae*: negative
- RPR: nonreactive
- HIV antibody test: negative
- Pregnancy test: positive

4. What would you tell Roberta about her HSV infection, based on clinical manifestations and test results?

Roberta most likely has an asymptomatic infection. Asymptomatic infection is defined as infection in which serum antibody is present, but there is no known history of clinical outbreaks.

Up to two-thirds of patients with identified asymptomatic HSV-2 infection actually have unrecognized symptomatic infection. Patients should be taught to recognize signs and symptoms of genital herpes. Roberta does have HSV-2 antibodies, but she has no symptoms and reports no previous episodes.

5. Would routine viral cultures during Roberta's pregnancy be recommended?

No. The results of viral cultures during pregnancy of women with or without visible herpetic lesions do NOT predict viral shedding at the time of delivery, and therefore routine viral cultures of pregnant women with recurrent genital herpes are NOT recommended.

[Slide 71]

Partner Management

Sex partner and exposure information:

Franklin Patterson

First sexual exposure: 16 months ago

Last sexual exposure: 1 month ago

History of genital herpes infection; first episode 8 years ago. No HSV testing or treatment at time of first episode or with subsequent episodes.
No history of other STDs.

6. Franklin reports genital lesions during Roberta's sixth month of pregnancy. Which laboratory tests should be performed on him?

Correct responses include the following:

HSV viral culture of the lesions. Viral cultures are the preferred HSV test for patients with genital ulcers or other mucocutaneous lesions. Tzanck stain of the lesions is insensitive and nonspecific, and should not be relied on for HSV diagnosis. Viral culture is preferred over DFA or EIA antigen detection tests when a patient has a genital lesion.

Darkfield microscopy or DFA-TP on genital lesions and RPR to test for syphilis. Syphilis testing should be considered for any patient presenting with genital lesions since genital lesions are a symptom of primary syphilis.

Testing for *C. trachomatis*, *N. gonorrhoeae*, and HIV. Because patients who have contracted an STD may be at greater risk for exposure to other STDs, it is useful to screen for other STDs, such as chlamydia, gonorrhea, and HIV.

[Slide 72]

Laboratory Results for Franklin

Franklin's laboratory test results are as follows:

HSV cultures: HSV-1 negative; HSV-2 positive

DNA probe for *Chlamydia trachomatis*: negative

Culture for *Neisseria gonorrhoeae*: negative

RPR: nonreactive

DFA: negative for *Treponema pallidum*

HIV antibody test: negative

7. What is an appropriate episodic treatment for Franklin?

Correct responses include the following:

Acyclovir 400 mg orally 3 times a day for 5 days

Acyclovir 200 mg orally 5 times a day for 5 days

Famciclovir 125 mg orally twice a day for 5 days

Valacyclovir 500 mg orally twice a day for 5 days

Valacyclovir 1 g orally once a day for 5 days

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Follow-Up

Roberta had no HSV symptoms during her pregnancy.

Roberta opted to take the acyclovir treatment in late pregnancy after a discussion with her certified nurse-midwife that included the following points:

- The safety of systemic acyclovir therapy in pregnant women has not been established.
- Preliminary data suggest that acyclovir treatment late in pregnancy might diminish the frequency of HSV occurrence at term that would necessitate an abdominal delivery.

At onset of labor, she reported no prodromal or other HSV symptoms and no lesions were found on examination.

After a 14-hour labor, she vaginally delivered a healthy 7.2 lb baby girl.

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8. What questions should ALL women beginning labor (regardless of their history of genital HPV infection) be asked?

All women beginning labor should be questioned about prodromal and other HSV symptoms and should be examined for lesions.

9. If Roberta had genital herpetic lesions at the onset of labor, should she deliver vaginally or abdominally? What is the risk to the infant?

Most specialists recommend that women with genital herpetic lesions at the onset of labor deliver abdominally to reduce the risk of neonatal herpes. However, abdominal delivery does not completely eliminate the risk for HSV transmission to the infant.

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10. Roberta is asymptomatic at the time of delivery. Is it medically appropriate for her to deliver vaginally?

Yes, women without symptoms of genital herpes or its prodrome can deliver vaginally.

11. If Roberta had acquired genital herpes around the time of delivery, would she be more or less likely to transmit genital herpes to her baby during a vaginal delivery than if she had a history of recurrent genital herpes?

If she had acquired genital herpes around the time of delivery, she would be more likely to transmit it to her baby than if she had a history of recurrent genital herpes. In vaginal delivery, transmission from an infected mother to the neonate occurs in up to 30%-50% of genital herpes infections acquired around the time of delivery and in <1% of recurrent infections.

TEST QUESTIONS

1. Genital herpes is:
 - a. A recurrent, life-long bacterial infection
 - b. A recurrent, life-long viral infection**
 - c. A transient infection caused by a protozoal organism
 - d. A transient viral infection
2. The majority of genital and perirectal herpetic outbreaks in the U.S. are caused by HSV-1.
 - a. True
 - b. False**
3. Which of the following statements is true about the prevalence and incidence of HSV-2?
 - a. There are over 1.6 million new cases of HSV-2 each year in the U.S.
 - b. Most people with HSV-2 have not been diagnosed.
 - c. Fifty percent or more of new cases are asymptomatic or unrecognized.
 - d. All of the above**
4. Which of the following statements is true about the transmission of HSV?
 - a. The average incubation period is 10 days.
 - b. Likelihood of transmission does not change with increased duration of infection.
 - c. HSV is readily inactivated by drying and soap and water.**
 - d. Most sexual transmission occurs while the source contact case is symptomatic.
5. In most cases of sexual transmission of genital HSV, the source case is asymptomatic.
 - a. True**
 - b. False
6. Sexual transmission of genital herpes is **less efficient** from
 - a. Women to men**
 - b. Men to women
 - c. Transmission efficiency is the same from men to women and from women to men.
7. Up to ___% of persons seropositive for HSV-2 antibody have no clinical history of anogenital herpes outbreaks.
 - a. 75
 - b. 80
 - c. 90**
 - d. 95
8. Which of the following statements is true about the pathogenesis of HSV?

- a. Up to 90% of persons seropositive for HSV-2 antibody have a clinical history of anogenital herpes outbreaks.
 - b. Most persons who are seropositive for HSV-2 with no symptoms still shed virus from the genital area intermittently.**
 - c. Reactivation and viral replication never occur.
 - d. All herpes viruses establish active infection in specific target cells.
9. Which clinical presentation is typical of the first episode with primary HSV-2 infection?
- a. No lesions or symptoms, HSV-1 antibodies may or may not be present, HSV-2 antibodies are present
 - b. Lesions present, symptoms usually mild, HSV-1 antibodies may or may not be present, HSV-2 antibodies are present
 - c. Lesions present, symptoms usually severe, HSV-1, HSV-2 antibodies are not present**
 - d. Lesions present, symptoms usually moderate, HSV-1 antibodies are present, HSV-2 antibodies are not present
10. The median duration of viral shedding in primary infection without treatment is:
- a. Approximately 4 days
 - b. Approximately 12 days**
 - c. 5-10 days
 - d. 2-4 weeks
11. All of the following are true of asymptomatic viral shedding, EXCEPT:
- a. Asymptomatic shedding occurs in almost all HSV-2 seropositive persons.
 - b. Rates of asymptomatic shedding are greater with HSV-1 than HSV-2.**
 - c. Rates of asymptomatic shedding with HSV-2 appear to be decreased by the presence of HSV-1 serum antibody.
 - d. The most common sites of asymptomatic shedding are the vulva and the perianal area in women and penile skin and the perianal area in men.
12. Which of the following is true about aseptic meningitis, a complication of genital herpes infection?
- a. It is more common in women than men.**
 - b. It is more common in HSV-1 than HSV-2.
 - c. It is more common in recurrent than primary infection.
 - d. It generally has severe neurologic sequelae.
13. Which of the following factors can affect the severity and frequency of clinical manifestations and recurrence rates of genital herpes infection?
- a. Viral type
 - b. Immune status of the host
 - c. Gender
 - d. All of the above**

14. Which of the following statements describes non-primary HSV infection?
- First infection ever with either HSV-1 or HSV-2
 - Disease is more severe than recurrent disease'
 - No serum antibody present when symptoms appear
 - Newly acquired infection with HSV-1 or HSV-2 in an individual previously seropositive to the other virus**
15. Primary infection without treatment lasts:
- 3-4 days
 - 5-7 days
 - 10-12 days
 - 2-4 weeks**
16. Which of the following statements is true about recurrent infection without treatment?
- Duration is shorter than primary infection.**
 - HSV-1 infection is much more likely to recur than HSV-2.
 - There are usually systemic symptoms associated with the recurrent infection.
 - HSV-2 will recur slightly more frequently and after a shorter period of time in women than in men.
17. Which of the following statements is true about asymptomatic viral shedding?
- Most HSV-2 is not transmitted during asymptomatic shedding.
 - Rates of asymptomatic shedding in HSV-2 seropositive persons are greatest in the first 6 months.
 - Presence of serum antibody of HSV-1 seems to decrease rates of asymptomatic shedding with HSV-2.**
 - Asymptomatic shedding occurs less frequently in men with established HSV-2 infection.
18. Which type of lab test is considered the gold standard for HSV diagnosis?
- Cytology
 - PCR assay
 - Antigen detection
 - Viral culture**
19. Which of the following tests is considered better than culture for diagnosing HSV if the lesions are healing?
- Type-specific serology
 - Antigen detection**
 - Tzanck smear
 - PCR assay
20. Type-specific serologic tests are recommended for all of the following reasons EXCEPT:

- a. To confirm clinical diagnosis
 - b. To diagnose unrecognized infection
 - c. To screen for HSV-1 or HSV-2 infection in the general population**
 - d. To manage sex partners of persons with genital herpes
21. Which of the following best describes antigen detection (DFA or EIA) testing?
- a. Preferred test for detecting HSV in spinal fluid; highly sensitive and specific; role in diagnosis of genital ulcer disease not well-defined
 - b. Rapid and highly specific; fairly sensitive for symptomatic shedders; may be better than culture for healing lesions**
 - c. Considered the gold standard; preferred test for patients with genital ulcers or other mucocutaneous lesions
 - d. Insensitive and nonspecific; should not be relied on for HSV diagnosis
22. Which of the following is true regarding systemic antiviral therapy?
- a. It partially controls symptoms and signs of herpes episodes when used to treat first clinical and recurrent episodes or when used as daily suppressive therapy.**
 - b. It reduces the frequency of genital herpes recurrences by 40%-50% when used as suppressive therapy for patients who have frequent recurrences.
 - c. It should never be provided to patients to self-initiate treatment when symptoms begin.
 - d. It is less effective than topical antiviral treatment for management of severe disease.
23. HSV systemic antiviral chemotherapy includes which of the following oral medications?
- a. Acyclovir
 - b. Valacyclovir
 - c. Famciclovir
 - d. All of the above**
24. Which of the following is true about episodic treatment of recurrent episodes of HSV disease?
- a. It can ameliorate or shorten the duration of lesions
 - b. Patient should self-initiate the medication
 - c. Successful treatment requires initiation of therapy within 1 day of lesion onset
 - d. All of the above**
25. All of the following are true of herpes in pregnancy, EXCEPT:
- a. The risk for transmission from infected mother to neonate is 30%-50% in women who acquire genital herpes near the time of delivery.
 - b. The risk for transmission from infected mother to neonate is <1% in women with histories of recurrent genital herpes or who acquire genital HSV during the first half of pregnancy.

- c. Most specialists recommend that women with recurrent genital herpetic lesions at the onset of labor be delivered abdominally.
 - d. Most specialists recommend that women with histories of recurrent genital herpes who have no symptoms or signs of genital herpes or its prodrome at the onset of labor be delivered abdominally.**
26. Asymptomatic sex partners of persons diagnosed with genital herpes should be:
- a. Counseled about the risk of asymptomatic transmission
 - b. Taught to recognize symptoms of genital herpes
 - c. Offered type-specific serologic testing for HSV infection
 - d. All of the above**
27. Patients with genital herpes should be informed that:
- a. Sexual transmission of HSV can occur during asymptomatic periods.
 - b. Stressful events may trigger recurrences.
 - c. The frequency of outbreaks generally decreases with increasing duration of the infection.
 - d. All of the above**
28. Which of the following is true of the relationship between HSV and HIV infection?
- a. Genital ulcers have no effect on the risk of HIV transmission and acquisition.
 - b. Lesions caused by HSV are uncommon in HIV-infected persons.
 - c. Increased doses of antiviral drugs have been demonstrated to be beneficial in HIV-infected persons with genital herpes.**
 - d. All of the above
29. Patient education should include all of the following, EXCEPT:
- a. HSV can be transmitted sexually during asymptomatic periods.
 - b. The frequency of outbreaks generally decreases with increasing duration of infection.
 - c. Condom use can protect against HSV transmission regardless of whether the infected area or site of infection is covered by the condom.**
 - d. Risks of neonatal infection should be explained to women and men.
30. Patients with genital herpes should be advised to:
- a. Abstain from sexual activity with uninfected partners when prodromal symptoms are present.
 - b. Inform their providers of their HSV status, if they are women of child-bearing age.
 - c. Inform future sex partners that they have genital herpes before initiating a sexual relationship.
 - d. All of the above**

RESOURCES

Publications

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Websites and Other Resources

1. CDC, Division of STD Prevention: www.cdc.gov/std
2. National Network of STD/HIV Prevention Training Centers: <http://depts.washington.edu/nnptc/>
3. 2002 CDC STD Treatment Guidelines (including downloadable version for Palm devices): <http://www.cdc.gov/STD/treatment/>
4. CDC National STD Hotline: 800-227-8922 or 800-342-2437; En Español: 800-344-7432; TTY for the Deaf and Hard of Hearing: 800-243-7889
5. CDC National Prevention Information Network (NPIN): www.cdcnpin.org
6. American Social Health Association (ASHA): www.ashastd.org