# eMedicine Specialties > Infectious Diseases > Viral Infections

# Herpes Simplex

**Michelle R Salvaggio, MD,** Assistant Professor, Department of Internal Medicine, Section of Infectious Diseases, University of Oklahoma College of Medicine; Medical Director of Infectious Diseases Institute, University of Oklahoma Health Sciences Center
**Larry I Lutwick, MD,** Professor of Medicine, State University of New York, Downstate Medical School; Director, Infectious Diseases, Veterans Affairs New York Harbor Health Care System, Brooklyn Campus; **Meena Seenivasan, MD,** Fellow, Department of Infectious Disease, State University of New York Health Science Center at Brooklyn; **Swati Kumar, MD,** Assistant Professor of Pediatrics, Division of Infectious Diseases, Medical College of Wisconsin, Consulting Staff, Children's Specialty Group, Children's Hospital of Wisconsin

Updated: May 27, 2009

# Introduction

## Background

Herpes simplex viruses are ubiquitous, host-adapted pathogens that cause a wide variety of disease states. Two types exist: herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2). Both are closely related but differ in epidemiology. HSV-1 is traditionally associated with orofacial disease, while HSV-2 is traditionally associated with genital disease; however, lesion location is not necessarily indicative of viral type.

Up to 80% of herpes simplex infections are asymptomatic. Symptomatic infections can be characterized by significant morbidity and recurrence. In immunocompromised hosts, infections can cause life-threatening complications.

The prevalence of HSV infection worldwide has increased over the last several decades, making it a major public health concern. Prompt recognition of herpes simplex infection and early initiation of therapy are of utmost importance in the management of the disease.

## Pathophysiology

HSV (both types 1 and 2) belongs to the family Herpesviridae and to the subfamily Alphaherpesvirinae. It is a double-stranded DNA virus characterized by the following unique biological properties:[1]

- Neurovirulence (the capacity to invade and replicate in the nervous system)
- Latency (the establishment and maintenance of latent infection in nerve cell ganglia proximal to the site of infection): In orofacial HSV infections, the trigeminal ganglia are most commonly involved, while, in genital HSV infection, the sacral nerve root ganglia (S2-S5) are involved.
- Reactivation: The reactivation and replication of latent HSV, always in the area supplied by the ganglia in which latency was established, can be induced by various stimuli (eg, fever, trauma, emotional stress, sunlight, menstruation), resulting in overt or covert recurrent infection and shedding of HSV. In immunocompetent persons who are at an equal risk of acquiring HSV-1 and HSV-2 both orally and

genitally, HSV-1 reactivates more frequently in the oral rather than the genital region. Similarly, HSV-2 reactivates 8-10 times more commonly in the genital region than in the orolabial regions. Reactivation is more common and severe in immunocompromised individuals.[2]

Dissemination of herpes simplex infection can occur in people with impaired T-cell immunity, such as in organ transplant recipients and in individuals with AIDS.

HSV is distributed worldwide. Humans are the only natural reservoirs, and no vectors are involved in transmission. Endemicity is easily maintained in most human communities owing to latent infection, periodic reactivation, and asymptomatic virus shedding.[3]

HSV is transmitted by close personal contact, and infection occurs via inoculation of virus into susceptible mucosal surfaces (eg, oropharynx, cervix, conjunctiva) or through small cracks in the skin. The virus is readily inactivated at room temperature and by drying; hence, aerosol and fomitic spread are rare.

## Frequency

## United Statealvato da Windows Internet Explorer 8> Subject: Herpes Simplex: [Print] - eMedicine Infectious Diseases Date: Fri, 4 Sep 2009 00:32:57 +0200 MIME-Version: 1.0 Content-Type: multipart/related; type="text/html"; boundary="----=_NextPart_000_004B_01CA2CF7.3FC94620" X-MimeOLE: Produced By Microsoft MimeOLE V6.00.2900.5579 This is a multi-part message in MIME format. ------=_NextPart_000_004B_01CA2CF7.3FC94620 Content-Type: text/html; charset="Windows-1252" Content-Transfer-Encoding: quoted-printable Content-Location: http://emedicine.medscape.com/article/218580-print



---

# eMedicine Specialties > Infectious Diseases > Viral Infections

# Herpes Simplex

**Michelle R Salvaggio, MD, Assistant Professor, Department of Internal Medicine, Section of Infectious Diseases, University of Oklahoma College of Medicine; Medical Director of Infectious Diseases Institute, University of Oklahoma Health Sciences Center**
**Larry I Lutwick, MD, Professor of Medicine, State University of New York, Downstate Medical School; Director, Infectious Diseases, Veterans Affairs New York Harbor Health Care System, Brooklyn Campus; Meena Seenivasan, MD, Fellow, Department of Infectious Disease, State University of New York Health Science Center at Brooklyn; Swati Kumar, MD, Assistant Professor of Pediatrics,**

**Division of Infectious Diseases, Medical College of Wisconsin, Consulting Staff, Children's Specialty Group, Children's Hospital of Wisconsin**

**Updated: May 27, 2009**

# Introduction

## Background

**Herpes simplex viruses are ubiquitous, host-adapted pathogens that cause a wide variety of disease states. Two types exist: herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2). Both are closely related but differ in epidemiology. HSV-1 is traditionally associated with orofacial disease, while HSV-2 is traditionally associated with genital disease; however, lesion location is not necessarily indicative of viral type.**

**Up to 80% of herpes simplex infections are asymptomatic. Symptomatic infections can be characterized by significant morbidity and recurrence. In immunocompromised hosts, infections can cause life-threatening complications.**

**The prevalence of HSV infection worldwide has increased over the last several decades, making it a major public health concern. Prompt recognition of herpes simplex infection and early initiation of therapy are of utmost importance in the management of the disease.**

## Pathophysiology

**HSV (both types 1 and 2) belongs to the family Herpesviridae and to the subfamily Alphaherpesvirinae. It is a double-stranded DNA virus characterized by the following unique biological properties:[1]**

- **Neurovirulence (the capacity to invade and replicate in the nervous system)**
- **Latency (the establishment and maintenance of latent infection in nerve cell ganglia proximal to the site of infection): In orofacial HSV infections, the trigeminal ganglia are most commonly involved, while, in genital HSV infection, the sacral nerve root ganglia (S2-S5) are involved.**
- **Reactivation: The reactivation and replication of latent HSV, always in the area supplied by the ganglia in which latency was established, can be induced by various stimuli (eg, fever, trauma, emotional stress, sunlight, menstruation), resulting in overt or covert recurrent infection and shedding of HSV. In immunocompetent persons who are at an equal risk of acquiring HSV-1 and HSV-2 both orally and genitally, HSV-1 reactivates more frequently in the oral rather than the genital region. Similarly, HSV-2 reactivates 8-10 times more commonly in the genital region than in the orolabial regions. Reactivation is more common and severe in immunocompromised individuals.[2]**

**Dissemination of herpes simplex infection can occur in people with impaired T-cell immunity, such as in organ transplant recipients and in individuals with AIDS.**

**HSV is distributed worldwide. Humans are the only natural reservoirs, and no vectors are involved in transmission. Endemicity is easily maintained in most human communities owing to latent infection, periodic reactivation, and asymptomatic virus shedding.[3]**

**HSV is transmitted by close personal contact, and infection occurs via inoculation of virus into susceptible mucosal surfaces (eg, oropharynx, cervix, conjunctiva) or through small cracks in the skin. The virus is readily inactivated at room temperature and by drying; hence, aerosol and fomitic spread are rare.**

## Frequency

### United States

**HSV is ubiquitous, and most individuals show some evidence of HSV infection. HSV-1 is usually acquired in childhood by contact with oral secretions that contain the virus. The presence of HSV-2 can be used as an indirect measure of sexual activity in some cases. Seroprevalence rates do not reflect how many of these individuals have or will have symptomatic episodes of HSV recurrence.**

**Seroprevalence: Antibodies to HSV-1 increase with age starting in childhood and correlate with socioeconomic status, race, and cultural group. By age 30 years, 50% of individuals in a high socioeconomic status and 80% in a lower socioeconomic status are seropositive. Antibodies to HSV-2 begin to emerge at puberty, correlating with the degree of sexual activity. The lifetime seroprevalence can be 20%-80%.[4]**

### International

**HSV is well distributed worldwide. An increase in seroprevalence of antibodies to HSV-2 has been documented throughout the world (including the United States) over the last 20 years.[1]**

## Mortality/Morbidity

**Morbidity and mortality rates associated with HSV infections are discussed in Complications. Overall, the mortality rate associated with herpes simplex infections is related to 3 situations: perinatal infection, encephalitis, and infection in the immunocompromised host.**

## Race

**The most recent national health survey conducted in the United States revealed a seroprevalence of HSV-2 antibodies in 45% of blacks, 22% of Mexican-Americans, and 17% of whites.[4]**

## Sex

**Seropositivity to antibodies to HSV-2 is more common in women (25%) than in men (17%).[4]**

## Age

**HSV-1 infections transmitted via saliva are common in children, although primary herpes gingivostomatitis can be observed at any age. HSV-2 infections are clustered perinatally (from a maternal episode at delivery) and primarily once sexual activity begins. HSV-2 genital infections in children can be an indication of sexual abuse. Increased age (after**

**onset of sexual activity) and total number of sexual partners are independent factors associated with increased seroprevalence of HSV-2 antibodies.[4]**

# Clinical

## History

**The clinical course of herpes simplex infection depends on the age and immune status of the host, the anatomic site of involvement, and the antigenic virus type. Primary herpes simplex virus (HSV)–1 and HSV-2 infections are accompanied by systemic signs, longer duration of symptoms, and higher rate of complications. Recurrent episodes are milder and shorter. Both HSV-1 and HSV-2 can cause similar genital and orofacial primary infections after contact with infectious secretions containing either HSV-1 (usually oral secretions) or HSV-2 (usually genital secretions).**

- **Acute herpetic gingivostomatitis[5]**
    - **This is a manifestation of primary HSV-1 infection that occurs in children aged 6 months to 5 years. Adults may also develop acute gingivostomatitis, but it is less severe and is associated more often with a posterior pharyngitis.**
    - **Infected saliva from an adult or another child is the mode of infection. The incubation period is 3-6 days.**
    - **Clinical features include the following:**
        - **Abrupt onset**
        - **High temperature (102-104°F)**
        - **Anorexia and listlessness**
        - **Gingivitis (This is the most striking feature, with markedly swollen, erythematous, friable gums.)**
        - **Vesicular lesions (These develop on the oral mucosa, tongue, and lips and later rupture and coalesce, leaving ulcerated plaques.)**
        - **Tender regional lymphadenopathy**
        - **Perioral skin involvement due to contamination with infected saliva**
    - **Course: Acute herpetic gingivostomatitis lasts 5-7 days, and the symptoms subside in 2 weeks. Viral shedding from the saliva may continue for 3 weeks or more.**
- **Acute herpetic pharyngotonsillitis**
    - **In adults, oropharyngeal HSV-1 infection causes pharyngitis and tonsillitis more often than gingivostomatitis.**
    - **Fever, malaise, headache, and sore throat are presenting features.**
    - **The vesicles rupture to form ulcerative lesions with grayish exudates on the tonsils and the posterior pharynx.**
    - **Associated oral and labial lesions occur in fewer than 10% of patients.**
    - **HSV-2 infection can cause similar symptoms and can be associated with orogenital contact or can occur concurrently with genital herpes.**
- **Herpes labialis[6]**
    - **This is the most common manifestation of recurrent HSV-1 infection. A prodrome of pain, burning, and tingling often occurs at the site, followed by the development of erythematous papules that rapidly develop into tiny, thin-walled, intraepidermal vesicles that become pustular and ulcerate. In**

**most patients, fewer than two recurrences manifest each year, but some individuals experience monthly recurrences.**

- **Maximum viral shedding is in the first 24 hours of the acute illness but may last 5 days.**

- **Genital herpes: The severity and frequency of the disease and the recurrence rate depend on numerous factors, including viral type, prior immunity to autologous or heterologous virus, gender, and immune status of the host.[7,2]**
- **Primary genital herpes**
  - **Primary genital herpes can be caused by both HSV-1 and HSV-2 and can be asymptomatic. The clinical features and course of primary genital herpes caused by both HSV-1 and HSV-2 are indistinguishable, but recurrences are more common with HSV-2.**
  - **Primary genital herpes is characterized by severe and prolonged systemic and local symptoms. The symptoms of persons with a first episode of secondary HSV-2 infection are less severe and of shorter duration.**
  - **Preexisting antibodies to HSV-1 have an ameliorating effect on disease severity caused by HSV-2.**
  - **Prior orolabial HSV-1 infection protects against genital HSV-1 but not HSV-2.**
  - **Symptoms of primary genital herpes are more severe in women, as are complications.**
  - **Clinical features: The incubation of primary genital herpes period is 3-7 days (range, 1 d to 3 wk). Constitutional symptoms include fever, headache, malaise, and myalgia (prominent in the first 3-4 d). Local symptoms include pain, itching, dysuria, vaginal and urethral discharge, and tender lymphadenopathy.**
  - **Clinical features in women: Herpetic vesicles appear on the external genitalia, labia majora, labia minora, vaginal vestibule, and introitus. In moist areas, the vesicles rupture, leaving exquisitely tender ulcers. The vaginal mucosa is inflamed and edematous. The cervix is involved in 70%-90% of cases and is characterized by ulcerative or necrotic cervical mucosa. Cervicitis is the sole manifestation in some patients. Dysuria may be very severe and may cause urinary retention. Dysuria is associated with urethritis, and HSV can be isolated in the urine. HSV-1 infection causes urethritis more often than does HSV-2 infection.**
  - **Clinical features in men: Herpetic vesicles appear in the glans penis, the prepuce, the shaft of the penis, and sometimes on the scrotum, thighs, and buttocks. In dry areas, the lesions progress to pustules and then encrust. Herpetic urethritis occurs in 30%-40% of affected men and is characterized by severe dysuria and mucoid discharge. The perianal area and rectum may be involved in persons who engage in anal intercourse, resulting in herpetic proctitis.**
  - **In men and women, the ulcerative lesions persist from 4-15 days until encrusting and reepithelialization occur. New lesions occur during the course of the illness in 75% of patients, usually forming in 4-10 days. The median duration of viral shedding is about 12 days.**
- **Recurrent genital herpes**
  - **The major morbidity of genital herpes is due to its frequent reactivation rate. In one study, 90% of patients reactivated within the first 12 months. In patients with HSV-2 infection, 38% had 6 recurrences in 1 year, and 20% had more than 10 recurrences in the first year.**

    - **Both subclinical and symptomatic reactivation is more common in HSV-2 infection than in HSV-1 infection. Sixty percent of patients with primary genital HSV-2 infection experience recurrences in the first year.**
    - **Patients who had severe primary genital herpes tend to have more frequent recurrences of longer duration.**
    - **Recurrent genital herpes is preceded by a prodrome of tenderness, pain, and burning at the site of eruption that may last from 2 hours to 2 days. In some patients, severe ipsilateral sacral neuralgia occurs.**
    - **In women, the vesicles are found on the labia majora, labia minora, or perineum. The lesions are often very painful. Fever and constitutional symptoms are uncommon. The lesions heal in 8-10 days, and viral shedding lasts an average 5 days. The symptoms are more severe in women than men.**
    - **In men, recurrent genital herpes presents as 1 or more patches of grouped vesicles on the shaft of the penis, prepuce, or glans. Urethritis is uncommon. Pain is mild, and lesions heal in 7-10 days. The frequency and severity of recurrences decrease with time.[2]**
- **Subclinical genital herpes**
    - **Most primary genital HSV infections are asymptomatic, with 70%-80% of seropositive individuals having no history of known genital herpes. However, upon education regarding the varied clinical manifestations, many patients recognize the symptoms of genital herpes.**
    - **Truly asymptomatic viral shedding may occur in 1%-2% of infected immunocompetent persons and may be as high as 6% in the first few months after acquisition of the infection.[3,8] This property is important when attempting to prevent transmission sexually or perinatally.**

## Physical

**This section describes physical examination findings of the herpetic lesion as it relates to primary and recurrent lesions of cutaneous or mucosal HSV infection. This can be related to either oral or genital infection.[1,2,5]**

- **Primary mucocutaneous HSV infections**
    - **Some primary infections are asymptomatic.**
    - **Primary (first-episode) infections manifest within several days of exposure to secretions containing viable virus.**
    - **Often painful, the lesions quickly progress to vesicles and can continue to erupt over 1-2 weeks.**
    - **The lesions are prominent and are often present internally on the mucosal surface of the oral or genital area, as well as on the surrounding skin.**
    - **Constitutional symptoms (fever, malaise, myalgias, and anorexia) are often prominent. Weight loss is not uncommon and is due either to illness or dysphagia (in primary gingivostomatitis).**
    - **Individual vesicles on mucosal surfaces break down rapidly, forming shallow painful ulcers (usually <8-10 mm in diameter). They may be covered with a white exudate that can be confused with mucosal candidiasis. Those on cutaneous surfaces remain as vesicles longer, only to evolve into crusted ulcers that heal within 5-7 days.**
- **Recurrent mucocutaneous HSV infections**

- Following the establishment of latency in the corresponding sensory nerve ganglion cells, HSV can cause recurrent infection that can be subclinical (manifesting as viral excretion without lesions) or overt (manifesting as mucosal or cutaneous lesions with viral excretion).
- Oral recurrences are often triggered by recognizable stimuli such as pyrexia (fever blisters and cold sores), stress, or sunburn. Genital recurrences are more likely to be linked to stress rather than to pyrexia. Females may relate a relationship to the menstrual cycle.
- Localized burning or paraesthesias may precede recurrent lesions. Unlike primary infection, constitutional symptoms are minimal in most cases.
- Recurrences last 3-7 days and can occur numerous times per year or once or twice in a lifetime. Overall, the number of yearly recurrences tends to decrease over time.[9]
- Although recurrent HSV infections may last much longer (>30 d) in immunocompromised hosts, such as individuals with AIDS, frequent recurrences are not necessarily a sign of an altered immune system.
- Because recurrences can be clinically unrecognizable, transmission to susceptible individuals can occur in the absence of overt lesions. In genital HSV infections, barrier protection should be used regardless of existing lesions, even in the absence of a history of genital HSV infection.
- Vesicles occurring in a sacral dermatomal distribution (zosteriform) can occur in recurrent genital HSV disease and be confused with herpes zoster. A history of similar recurrences should alert the clinician to this possibility.
- Sacral HSV infection recurrences also may present with signs and symptoms of meningeal inflammation; and, in fact, a picture consistent with aseptic meningitis can be found upon examination of the cerebrospinal fluid (CSF).[10]

## Causes

- HSV is transmitted via close personal contact.
- HSV infection occurs via inoculation of virus into susceptible mucosal surfaces (eg, oropharynx, cervix, conjunctiva) or through small cracks in the skin.
- The virus is inactivated readily at room temperature and by drying; hence, aerosol and fomitic spread are rare.
- HSV-1 is transmitted chiefly by contact with infected saliva, whereas HSV-2 is transmitted sexually or from a mother's genital tract infection to her newborn. However, lesion location does not always indicate viral type.

# Differential Diagnoses

**Candidiasis**
**Chancroid**
**Hand-Foot-and-Mouth Disease**
**Herpes Zoster**
**Syphilis**

## Other Problems to Be Considered

**Oral ulcerative disease**

**Oral candidiasis**
**Hand-foot-and-mouth disease**
**Aphthous ulcers**

**Genital ulcerative disease**

**Syphilis**
**Chancroid**

# Workup

## Laboratory Studies

- **Herpes simplex virus (HSV) infection is best confirmed by isolation of the virus in tissue culture (the criterion standard for diagnosis). Tissue culture success is operator-dependent, but this modality can yield positive results within 48 hours of inoculation.**
    - **Characteristic cytopathic effect with ballooning of cells and cell death are observed, and death of the entire monolayer of cells may be rapid.**
    - **Immunofluorescent staining of the tissue culture cells can be used to quickly identify HSV and can distinguish between types 1 and 2.**
- **The characteristic cytologic changes induced by HSV can be demonstrated in Tzank smears (see Procedures); however, this procedure does not distinguish between HSV-1 and HSV-2.**
    - **Rapid diagnosis (usually within an hour) is possible based on the histological appearance of the lesion.**
    - **Multinucleated giant cells and epithelial cells containing eosinophilic intranuclear inclusion bodies distinguish the lesions of herpesviruses.**
    - **Punch biopsy provides more reliable material for histological examination, particularly when lesions are infected with bacteria and fungi.**
- **Detection of HSV DNA in clinical specimens is possible with polymerase chain reaction (PCR) techniques.**
    - **In HSV encephalitis, PCR using CSF provides a rapid, noninvasive diagnostic technique that is as sensitive as brain biopsy.[11]**
    - **PCR has been used to detect HSV-2 as the cause of recurrent meningitis (Mollaret) and has shown a strong association between HSV-1 and Bell's palsy.**
    - **PCR can be used to detect asymptomatic viral shedding.**
- **Direct fluorescent antigen (DFA): Cells scraped from ulcer bases can be stained with a direct fluorescent antibody, used to distinguish HSV-1 from HSV-2. Additionally, tissue culture cells can also be stained (see above). This procedure can usually be performed within 2-3 hours.**
- **Antibody testing can demonstrate a primary seroconversion, particularly with HSV-1 in childhood.[1]**
    - **Because of sero–cross-reactivity, HSV-1 and HSV-2 are not generally distinguishable unless a glycoprotein G antibody assay is available. Testing for HSV-specific immunoglobulin M (IgM) antibodies is not available.**

    - **Antibody titer increases generally do not occur during recurrences of HSV infection. Therefore, the test is generally not used for the diagnosis of mucocutaneous HSV relapse.**
    - **Antibody testing has been the mainstay of large-scale epidemiologic studies.**

## Imaging Studies

- **Brain imaging studies in HSV encephalitis generally demonstrate focal localization in the temporal area that is associated with edema and contrast enhancement.**

## Procedures

- **Tzanck preparation is a time-honored procedure for assisting in the diagnosis of cutaneous herpesvirus infections. However, it does not easily distinguish HSV-1, HSV-2, and varicella-zoster virus.**
    - **Typically, an intact vesicle is used from which the vesicular fluid is aspirated by puncture with a sterile tuberculin syringe. This fluid can be used for viral culture or PCR.**
    - **Aspiration should facilitate complete collapse of the vesicle because it is not multiloculated as cutaneous poxvirus infections can be.**
    - **After aspiration, the vesicle should be unroofed aseptically.**
    - **Using a sterile instrument, the floor of the newly produced ulcer can then be scraped. The obtained material can be spread on a glass microscope slide and then dried and fixed for staining.**
    - **Staining can be performed with a Papanicolaou smear stain or, alternatively, whatever is available will suffice (eg, Gram, Giemsa, or Wright stain).**
    - **A positive result is the finding of multinucleate giant cells.**
- **DFA: Using appropriate immunofluorescent antibody reagents, the smear can be used to distinguish different herpesviruses and nonherpesviruses that may be present (eg, vaccinia, smallpox).**

# Treatment

## Medical Care

- **Overall, medical treatment of herpes simplex virus (HSV) infection is centered around specific antiviral treatment. While the same medications are active against HSV-1 and HSV-2, the location of the lesions and the chronicity (primary or reactivation) of the infection dictate the dosage and frequency of medication. It is important to note that life-threatening HSV infections in immunocompromised patients and HSV encephalitis require high-dose intravenous acyclovir, often started empirically.[12]**
- **When constitutional effects such as fever occur, symptomatic treatment can be used.**
- **Appropriate wound care is needed, and treatment for secondary bacterial skin infections may be required.**

## Consultations

- **Consultation with a dermatologist may be beneficial in cases of atypical lesions.**
- **In immunocompromised patients with invasive HSV infection, consultation of specialty associated with the organ system affected should be sought early (eg, pulmonologist for possible HSV pneumonitis) in order to aid in diagnosis.**

# Medication

**The goals of pharmacotherapy are to reduce morbidity and to prevent complications.**

## Antivirals

**Nucleoside analogs are phosphorylated initially by viral thymidine kinase to eventually form a nucleoside triphosphate. These molecules inhibit herpes simplex virus (HSV) polymerase with 30-50 times the potency of human alpha-DNA polymerase.**

### Penciclovir (Denavir)

**Inhibitor of DNA polymerase in HSV-1 and HSV-2 strains, inhibiting viral replication.**

### Dosing

**Adult**

**Apply q2h while awake for 4 d at first sign of symptom; for oral-facial HSV only**

**Pediatric**

**Administer as in adults**

### Interactions

**None reported**

### Contraindications

**Documented hypersensitivity; previous adverse reaction to famciclovir**

### Precautions

**Pregnancy**

**B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals**

**Precautions**

**May experience mild erythema**

## Acyclovir (Zovirax)

**Synthetic purine nucleoside analogue with activity against a number of herpesviruses, including herpes simplex and varicella-zoster. Highly selective for virus-infected cells because of its high affinity for viral thymidine kinase enzyme. This effect serves to concentrate acyclovir monophosphate into virus-infected cells. The monophosphate then is metabolized into the triphosphate active form by cellular kinases.**
**Double dose is suggested for herpes simplex proctitis or ocular infections. Ocular infections also can be treated with topical acyclovir. Oral suspension available (40 mg/mL).**

## Dosing

### Adult

**First episode mucocutaneous herpes simplex: 200 mg PO 5 times daily or 400 mg tid for 7-10 d or until clinical resolution occurs**
**Recurrent genital herpes: 200 mg PO five times daily for 5 d**
**Chronic suppressive therapy: 400 mg bid or 200 mg 3-5 times daily; reevaluate after 1 y**
**Herpes simplex encephalitis: 10 mg/kg IV q8h for 10-14 d**
**Severe infection in immunocompromised host: 5-10 mg/kg IV q8h for 5-10 d**

### Pediatric

**First episode mucocutaneous herpes simplex: 20-30 mg/kg/d in 5 divided doses for 7-10 d**
**Severe infections in immunocompromised children: 10 mg/kg/d IV q8h for 7 d**
**Herpes encephalitis: 20 mg/kg IV q8h for 10-14 d**

## Interactions

**Concomitant use of probenecid or zidovudine prolongs half-life and increases CNS toxicity**

## Contraindications

**Documented hypersensitivity**

## Precautions

### Pregnancy

**B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals**

### Precautions

**Renal dysfunction (usually reversible) can occur during high-dose IV administration (primarily related to drug crystalluria); effect can be minimized by slow infusion and adequate hydration; neurological symptoms, including lethargy, agitation, myoclonus, or**

**seizures is observed in <1% of patients; appears to be dose-related phenomenon with increased risk with azotemia**

## Valacyclovir (Valtrex)

**Prodrug rapidly converted to the active drug acyclovir. More expensive but has a more convenient dosing regimen than acyclovir.**

## Dosing

**Adult**

**First episode herpes simplex: 1 g bid for 10 d, preferably beginning within 48 h of onset**
**Recurrent episode herpes simplex: 500 mg bid for 5 d beginning within 24 h of onset**
**Suppressive dosing for HSV: 500 mg to 1 g/d**

**Pediatric**

**Not established**

## Interactions

**Probenecid, zidovudine, or cimetidine coadministration prolongs half-life and increases CNS toxicity of valacyclovir**

## Contraindications

**Documented hypersensitivity**

## Precautions

**Pregnancy**

**B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals**

**Precautions**

**Caution in renal failure and coadministration of nephrotoxic drugs; associated with onset of hemolytic uremic syndrome**

## Famciclovir (Famvir)

**Prodrug that when biotransformed into active metabolite, penciclovir, may inhibit viral DNA synthesis/replication. Used against herpes simplex and varicella-zoster viruses.**

### Dosing

**Adult**

**Recurrent genital HSV: 125 mg PO bid for 5 d**
**Recurrent genital HSV in HIV-infected patients: 500 mg PO bid for 7 d**
**Suppression of frequent recurrence of genital HSV: 250 mg PO bid up to 12 mo**

**Pediatric**

**Not established**

### Interactions

**Coadministration of probenecid or cimetidine may increase toxicity; coadministration increases bioavailability of digoxin**

### Contraindications

**Documented hypersensitivity**

### Precautions

**Pregnancy**

**B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals**

**Precautions**

**Caution in renal failure or coadministration of nephrotoxic drugs; dosage adjustment in renal impairment recommended (half-life prolonged by 5-6 times if CrCl <20 mL/min)**

# Follow-up

## Deterrence/Prevention

- **Because of the ubiquitous and cosmopolitan nature of herpes simplex virus (HSV), avoiding contact with individuals who (often asymptomatically) are excreting the virus in saliva or genital secretions is difficult. Daily antiviral therapy can be given to reduce episodes of asymptomatic genital shedding and to further reduce the risk of transmission; however, it is unclear how long this should be administered.**
- **Although not easily applicable to oral-oral contact, barrier protection using latex condoms is recommended to minimize exposure to genital HSV infections.**
- **Because HSV genital ulcers may occur outside of areas covered by the condom, transmission can occur in those areas.**

- **Herpetic whitlow can be avoided with latex gloves when health care workers insert their hands into the oral cavity of patients. Transmission of genital virus to the hand can occur during unprotected finger-genital contact during sexual activities.**
- **Suppressive antiviral therapy can be used in individuals with frequent and/or particularly symptomatic relapses.**

## Complications

- **Bacterial and fungal superinfections are not uncommon.**
    - **Balanitis can occur in an uncircumcised male as a result of bacterial infection of the herpetic ulcers.**
    - **Candidal vaginitis has been described in as many as 10% of women with primary genital herpes, particularly in women with diabetes. Care should be taken to confirm the diagnosis of candidiasis, as ulcerative herpetic disease can have whitish mucosal lesions that can be confused with yeast infection.**
- **Ocular infections**
    - **This complication is not uncommon in children as a result of autoinoculation during acute herpetic gingivostomatosis or asymptomatic oropharyngeal HSV infection.**
    - **Ocular infection is caused primarily by HSV-1, except in neonates, in whom it may be caused by HSV-2, and manifests as unilateral follicular conjunctivitis or as acute herpetic keratoconjuctivitis with dendritic corneal ulcers.[13]**
    - **Recurrences occur in as many as 25% of patients and can be associated with progressive scarring of the cornea. HSV has been the leading infectious cause of blindness in the United States.**
- **Skin infections: Various cutaneous complications related to HSV can occur.**
    - **Eczema herpeticum: This occurs in individuals with underlying dermatitis and may be localized (which can be confused with herpes zoster) or disseminated. The process can also occur in patients with extensive skin breakdown as with burns, pemphigus, or Sézary syndrome.**
    - **Herpetic whitlow: HSV infections of the fingers occur at or near the cuticle or at other sites associated with trauma. When involving the nail area, it has been confused with a bacterial felon and been subjected, inappropriately, to incision and drainage. Herpetic whitlow is associated with HSV-1 in health care workers and children related to saliva exposure and with HSV-2 related to digital-genital exposure.**
    - **Herpes gladiatorum: Scattered cutaneous HSV-1 lesions have been observed in wrestlers who have had viral contact through exposure to infectious saliva during a match.**
- **Visceral infections: HSV infection of the visceral organs usually results from viremia, and multiple organ involvement is common. This may occur during otherwise asymptomatic primary infections and sometimes in seemingly immunocompetent hosts.**
    - **In most cases of disseminated herpes, the lesions are confined to the skin; however, fatal visceral dissemination can occur with or without vesicular skin lesions. Multiple organs are involved, but fulminant HSV hepatitis is usually clinically prominent.**
    - **It is associated with leukopenia, thrombocytopenia, and disseminated intravascular coagulation.**

- **Disseminated HSV-1 and HSV-2 infections can also result in herpetic esophagitis, adrenal necrosis, interstitial HSV pneumonitis, HSV cystitis, HSV arthritis, HSV meningitis, and HSV encephalitis.**

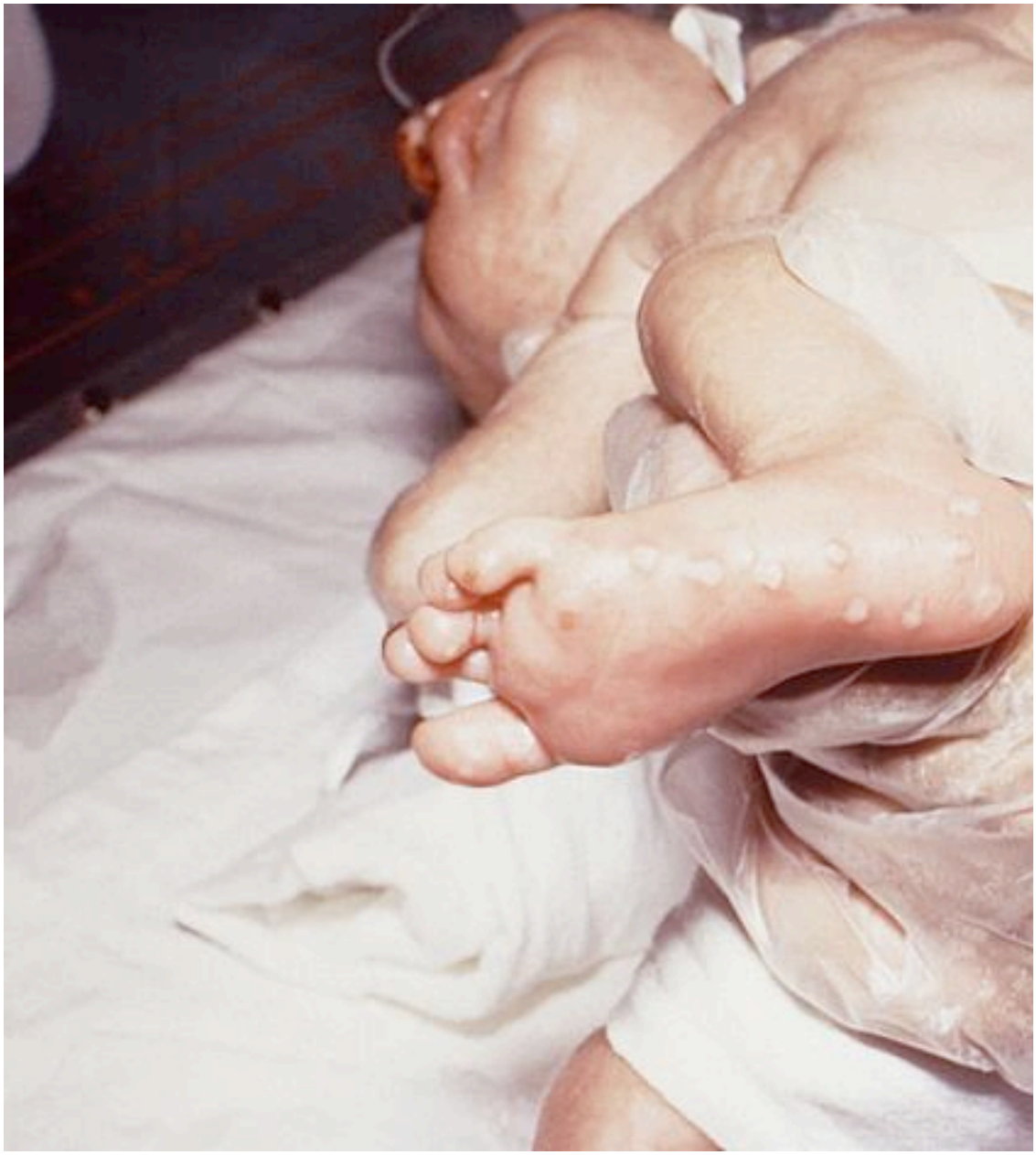
- **Central nervous system complications[10,14]**
  - **Aseptic meningitis: This condition is an acute, generally benign lymphocytic meningitis. In one series, 36% of women and 13% of men with primary genital HSV-2 infection had meningeal symptoms on two consecutive examinations. It is more common with HSV-2 infection. Meningeal symptoms usually start 3-12 days after the onset of genital lesions; they reach a maximum 2-4 days into the illness and recede over 2-4 days. Signs and symptoms of encephalitis are unusual, and neurological sequelae are rare. HSV-1 also has been identified by PCR in the CSF of patients with benign lymphocytic recurrent meningitis (Mollaret meningitis), suggesting that HSV may be the cause of this so-called idiopathic syndrome.**
  - **Ganglionitis and myelitis: Genital and anorectal HSV infections may be complicated by urinary retention, sacral neuralgia, and sacral anesthesia. This is due to associated ganglionitis and radiculitis. The symptoms usually resolve in 1-2 weeks. Transverse myelitis is rarely reported.**
  - **Herpes simplex encephalitis: This is an acute necrotizing viral encephalitis that, beyond the neonatal period, is nearly always caused by HSV-1. It accounts for 10%-20% of all cases of encephalitis and is the most common cause of sporadic acute necrotizing encephalitis in the United States. Herpes simplex encephalitis occurs as a primary infection in about 50% of cases and may be due to recurrent infection or to reinfection with a different strain of HSV-1 in the remainder. Clinical features include the following:**
    - **Nonspecific findings common to all forms of encephalitis, which include headache, signs of meningeal irritation, altered mental status, and generalized seizures**
    - **Changes referable to focal necrosis of the orbitofrontal and temporal cortex and the limbic system, including anosmia, memory loss, olfactory and gustatory hallucinations, and focal seizures**
    - **Rapid development of hemiparesis and coma may occur. In some patients, the clinical picture is protracted, mimicking acute psychosis or delirium tremens.**
    - **The CSF has moderate pleocytosis with mixed mononuclear cells and polymorphonuclear cells, moderate RBC counts, and mildly elevated protein levels with normal glucose levels.**
    - **MRI is the most sensitive imaging procedure.**
    - **The most sensitive noninvasive method of diagnosis is the demonstration of HSV DNA by PCR.**
    - **The mortality rate is high (70%) in untreated patients. Even with treatment, a high incidence of neurological sequelae remains.**

- **Genital herpes and pregnancy**
  - **Recurrent genital herpes is similar in pregnant and nonpregnant women, although an increase in the number of recurrences in the course of pregnancy may occur.**
  - **Recurrent genital herpes accounts for 1%-2% of all cases of neonatal herpes. Cesarean delivery is recommended in mothers who have active genital lesions during labor. However, presence of active genital lesions is**

**not a good indicator of HSV viral shedding.[15] Thus the American College of Obstetricians and Gynecologists (ACOG) recommends that suppressive antiviral therapy be given to all women with a history of recurrent genital HSV in the last 4 weeks of pregnancy.[16]**

- **Primary genital infection during pregnancy**
  - **First-episode infections have more severe consequences to the mother and infant. Thus, identification of women at risk for primary infection (seronegative for HSV-2) is paramount.**
  - **Serological discordance between partners may be 15%-20%, so that the risk of a seronegative mother becoming infected from the father during pregnancy is 10%-15%.**
  - **Pregnant women may have widely disseminated infection with a high mortality rate (50%).**
  - **Infection in the third trimester of pregnancy is associated with neonatal HSV infections, intrauterine growth retardation, and prematurity.**

- **Neonatal HSV disease**
  - **Ninety percent of infections are acquired perinatally, 5%-8% are acquired congenitally, and a few are acquired postnatally.**
  - **Neonatal HSV infection is caused by contact with infected genital secretions.**
  - **In 70% of mothers, the infection is asymptomatic. The risk of transmission from a mother with primary infection is about 50%.[17]**
  - **Neonates and infants (aged <6 wk) have a very high frequency of visceral and CNS infections. Without therapy, the mortality rate is 65%, and a high degree of neurological sequelae exists.**
  - **The disease may be confined to the skin, eyes, or mouth, or it may manifest as encephalitis or disseminated visceral disease involving the lungs, liver, heart, adrenals, and skin.**



**This neonate displayed a maculopapular outbreak on his feet due to congenitally acquired herpes simplex virus infection. Courtesy of the CDC/Judith Faulk.**

- **Copathogenesis with HIV: Multiple studies have shown that the presence of antibodies to HSV-2 increases the risk of becoming infected with HIV, independent of the presence of genital ulcers.[18] While early studies in Africa have demonstrated a reduction of HIV viral load in patients with HIV infection receiving therapy directed toward HSV infection, the mechanism is unclear.[19,20] The association between HIV and HSV may change the epidemiologic approach to sexually transmitted diseases worldwide.**

## Patient Education

- **For excellent patient education resources, visit eMedicine's Sexually Transmitted Diseases Center and Teeth and Mouth Center. Also, see eMedicine's patient education articles Genital Herpes, Oral Herpes, Birth Control Overview, and Birth Control FAQs.**

# Miscellaneous

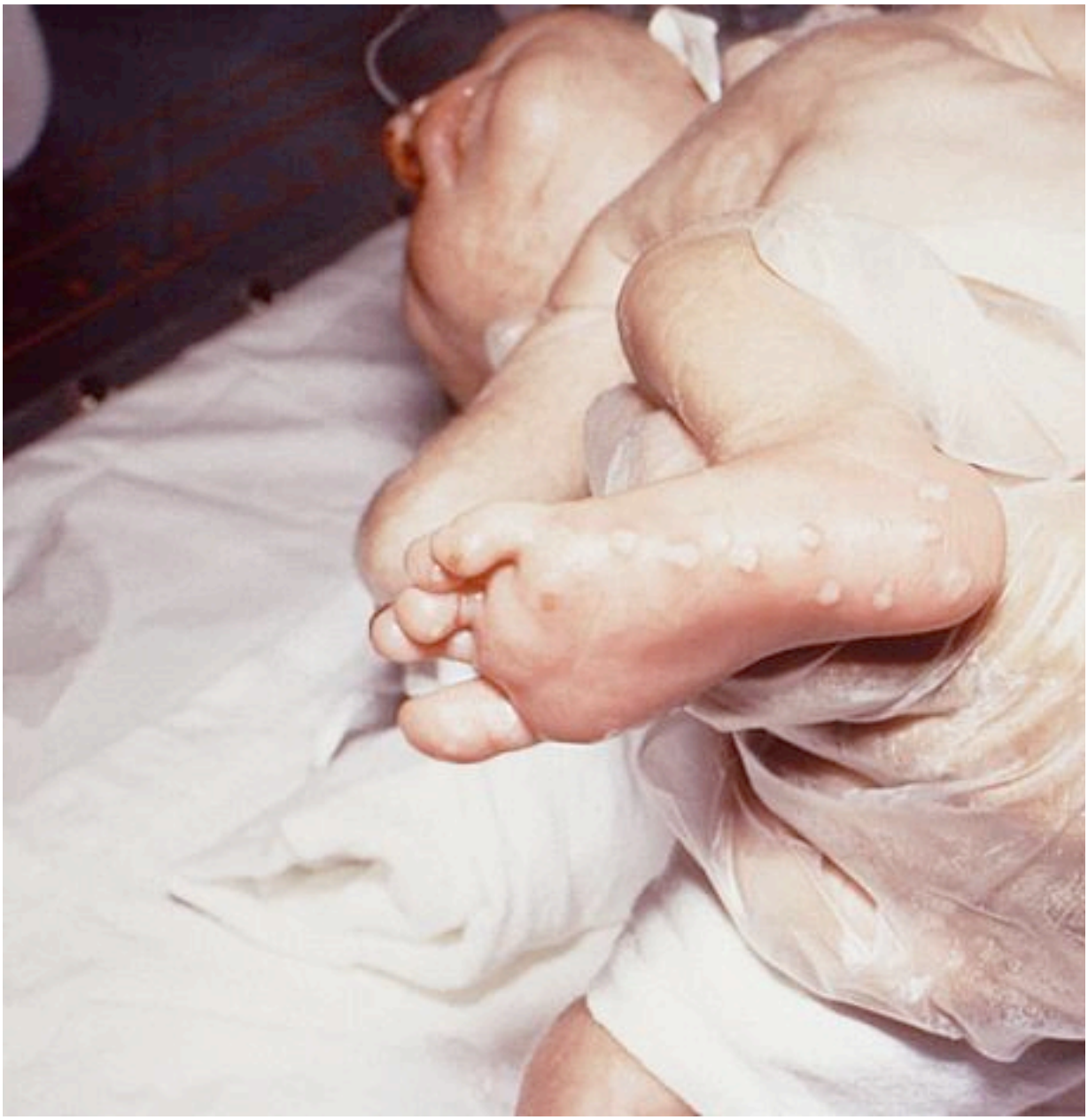
## Medicolegal Pitfalls

- **Lawsuits over sexual transmission**
  - **Legal actions have been taken over transmission of herpes simplex virus (HSV) through unprotected sexual activity.**
  - **Demonstration that both partners are infected with the same type of HSV is not adequate to prove that one partner infected the other.**
  - **The use of restriction endonucleases, which lyse DNA at very specific base sequences, can strongly suggest an epidemiologic link between 2 isolates but does not indicate the direction of the transmission.**
  - **Genital HSV-2 infection in young children may be an indicator of sexual abuse in parallel to gonococcal infections.**
- **Recognition of HSV encephalitis**
  - **Because prompt treatment of HSV encephalitis appears to minimize residual neurologic damage and the risk of death, considering this diagnosis early is important in appropriate cases. Perform necessary diagnostic tests and institute early, usually empirical, antiviral therapy.**
  - **However, unsatisfactory outcomes can occur, even with the early use of antiviral treatment.**
- **Prevention of perinatal HSV infection: In order to reduce the risk of perinatal HSV, ACOG recommends suppressive antiviral be given to any women with a known history of genital HSV, for the last 4 weeks of gestation[16]; however, large-scale studies of long-term effects in children of women who received antivirals in utero are lacking.[21,22]**

## Special Concerns

- **Development of antiviral drug resistance[23,24]**
  - **Antiviral resistance of HSV can be selected for both in vitro and in vivo.**
  - **Once these isolates are present, commonly representing thymidine kinase–negative mutants, the usual treatments are not likely to be effective, and alternate modalities of therapy must be sought.**
  - **The use of prolonged suppressive therapy for HSV infection no doubt contributes substantially to the risk of developing resistance.**
  - **Because of the possibility of developing resistance, the decision to use chronic suppression (or patient-driven relapse treatment) must be made while carefully balancing the positive effect of suppression or any likely minimal effect of therapy on an already overt mucocutaneous relapse against the potential for resistance.**

# Multimedia



**Media file 1: This neonate displayed a maculopapular outbreak on his feet due to congenitally acquired herpes simplex virus infection. Courtesy of the CDC/Judith Faulk.**

# References


1. Corey L. Herpes Simplex Virus. In: Mandell GI, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases*. Vol 2. 6th ed. Pennsylvania: Elsevier; 2005:1762-80.
2. Kimberlin DW, Rouse DJ. Clinical practice. Genital herpes. *N Engl J Med*. May 6 2004;350(19):1970-7. [Medline].

3. Mark KE, Wald A, Magaret AS, Selke S, Olin L, Huang ML. Rapidly cleared episodes of herpes simplex virus reactivation in immunocompetent adults. *J Infect Dis*. Oct 15 2008;198(8):1141-9. [Medline].
4. Fleming DT, McQuillan GM, Johnson RE, et al. Herpes simplex virus type 2 in the United States, 1976 to 1994. *N Engl J Med*. Oct 16 1997;337(16):1105-11. [Medline].
5. Arduino PG, Porter SR. Oral and perioral herpes simplex virus type 1 (HSV-1) infection: review of its management. *Oral Dis*. May 2006;12(3):254-70. [Medline].
6. Spruance SL, Overall JC Jr, Kern ER, Krueger GG, Pliam V, Miller W. The natural history of recurrent herpes simplex labialis: implications for antiviral therapy. *N Engl J Med*. Jul 14 1977;297(2):69-75. [Medline].
7. Corey L, Adams HG, Brown ZA, Holmes KK. Genital herpes simplex virus infections: clinical manifestations, course, and complications. *Ann Intern Med*. Jun 1983;98(6):958-72. [Medline].
8. Wald A, Zeh J, Selke S, Ashley RL, Corey L. Virologic characteristics of subclinical and symptomatic genital herpes infections. *N Engl J Med*. Sep 21 1995;333(12):770-5. [Medline].
9. Benedetti JK, Zeh J, Corey L. Clinical reactivation of genital herpes simplex virus infection decreases in frequency over time. *Ann Intern Med*. Jul 6 1999;131(1):14-20. [Medline].
10. Sköldenberg B, Jeansson S, Wolontis S. Herpes simplex virus type 2 and acute aseptic meningitis. Clinical features of cases with isolation of herpes simplex virus from cerebrospinal fluids. *Scand J Infect Dis*. 1975;7(4):227-32. [Medline].
11. Aurelius E, Johansson B, Skoldenberg B, Staland A, Forsgren M. Rapid diagnosis of herpes simplex encephalitis by nested polymerase chain reaction assay of cerebrospinal fluid. *Lancet*. Jan 26 1991;337(8735):189-92. [Medline].
12. Gnann JW, Salvaggio MR. Drugs for Herpesvirus Infections. In: Cohen J, Powderly W, eds. *Infectious Diseases*. Vol 2. 2nd ed. New York: Mosby; 2004:1895-909.
13. Green LK, Pavan-Langston D. Herpes simplex ocular inflammatory disease. *Int Ophthalmol Clin*. Spring 2006;46(2):27-37. [Medline].
14. Whitley RJ. Herpes simplex virus infections of the central nervous system. A review. *Am J Med*. Aug 29 1988;85(2A):61-7. [Medline].
15. Gardella C, Brown ZA, Wald A, Morrow RA, Selke S, Krantz E. Poor correlation between genital lesions and detection of herpes simplex virus in women in labor. *Obstet Gynecol*. Aug 2005;106(2):268-74. [Medline].
16. American College Obstetricians and Gynecologists. Management of herpes in pregnancy. *ACOG Practice Bulletin*. October 1999;Number 8:644-652.
17. Brown ZA, Wald A, Morrow RA, Selke S, Zeh J, Corey L. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. *JAMA*. Jan 8 2003;289(2):203-9. [Medline].
18. Corey L, Wald A, Celum CL, Quinn TC. The effects of herpes simplex virus-2 on HIV-1 acquisition and transmission: a review of two overlapping epidemics. *J Acquir Immune Defic Syndr*. Apr 15 2004;35(5):435-45. [Medline].
19. Nagot N, Ouedraogo A, Foulongne V, Konate I, Weiss HA, Vergne L. Reduction of HIV-1 RNA levels with therapy to suppress herpes simplex virus. *N Engl J Med*. Feb 22 2007;356(8):790-9. [Medline].
20. [Best Evidence] Baeten JM, Strick LB, Lucchetti A, Whittington WL, Sanchez J, Coombs RW, et al. Herpes simplex virus (HSV)-suppressive therapy decreases plasma and genital HIV-1 levels in HSV-2/HIV-1 coinfected women: a randomized, placebo-controlled, cross-over trial. *J Infect Dis*. Dec 15 2008;198(12):1804-8. [Medline].

21. **[Best Evidence] Andrews WW, Kimberlin DF, Whitley R, Cliver S, Ramsey PS, Deeter R. Valacyclovir therapy to reduce recurrent genital herpes in pregnant women. *Am J Obstet Gynecol*. Mar 2006;194(3):774-81. [Medline].**
22. **[Best Evidence] Sheffield JS, Hill JB, Hollier LM, Laibl VR, Roberts SW, Sanchez PJ. Valacyclovir prophylaxis to prevent recurrent herpes at delivery: a randomized clinical trial. *Obstet Gynecol*. Jul 2006;108(1):141-7. [Medline].**
23. **Hasegawa T, Kawana T, Okuda T, Horii M, Tsukada T, Shiraki K. Susceptibility to acyclovir of herpes simplex virus isolates obtained between 1977 and 1996 in Japan. *J Med Virol*. Jan 2001;63(1):57-63. [Medline].**
24. **Rabella N, Otegui M, Labeaga R, et al. Antiviral susceptibility of Herpes simplex viruses and its clinical correlates: a single center's experience. *Clin Infect Dis*. Apr 15 2002;34(8):1055-60. [Medline].**