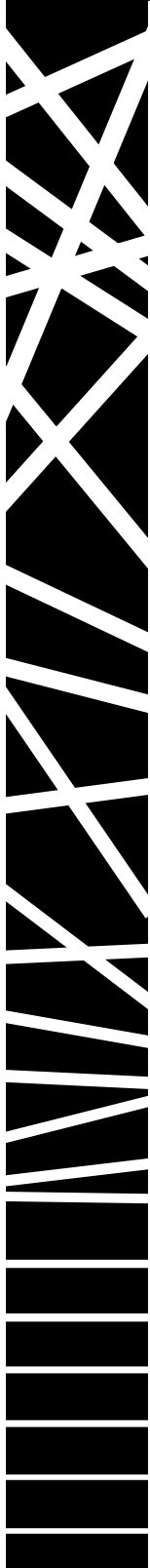


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HERPES SIMPLEX VIRUS (HSV) INFECTIONS



STD/HIV
Prevention
Training
Center of New England

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HERPES SIMPLEX VIRUS (HSV) INFECTIONS

OBJECTIVES

1. Describe the prevalence of HSV infections.
2. Describe the transmission, pathogenesis, natural history and clinical manifestations of HSV infections.
3. Define the laboratory methods available and their application for the diagnosis of HSV given specific case examples.
4. Discuss available therapies for the management of primary and recurrent HSV infections.
5. Describe the incidence of neonatal herpes, risk factors for transmission to newborns, evaluation/management of HSV during pregnancy and management of delivery.
6. Discuss the relationship of HSV and HIV, and the management of HSV in HIV infected persons.
7. Deliver appropriate counseling messages based on current transmission and treatment information.

1.0 BIOLOGY OF GENITAL HERPES

Herpes virus is a member of the **Human Herpes viruses (herpetoviridae)**, which include: herpes simplex virus type 1 (HSV-1), herpes virus simplex type 2 (HSV-2), varicella zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpes virus HHV-6, HHV-7, HHV-8. It is a large **double-stranded DNA** virus surrounded by an envelope of lipid glycoprotein.

50% DNA homology between HSV-1 and HSV-2.

1.1 PATHOGENESIS OF DISEASE

Viral **inoculation** occurs through **microabrasions** during oral, vaginal or rectal sex with infected partner. Infection of epithelial cells occurs with rapid intranuclear viral replication. Changes include focal necrosis, ballooning and degeneration of cells. Hallmark: **multinucleated** giant cell and Cowdry type A bodies = eosinophilic intranuclear inclusion.

All members of this species establish **latent infection** in specific target cells. The infection persists despite the host immune response, often with recurrent disease. **Re-infection can occasionally occur despite immunity.**

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PRIMARY INFECTION

HSV ascends sensory nerves (along peripheral sensory nerve axons) and establishes **latency for life** within sensory nerve cell bodies in the dorsal root ganglia.

In severe primary infection, particularly in immunocompromised hosts, viral replication may lead to **viremia** and visceral dissemination.

Primary infection is controlled by development of effective cell-mediated immunity.

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RECURRENCE

Is triggered by **known factors** (exposure to sunlight and ultraviolet radiation, fever, trauma, diminished cellular immunity, emotional stress) and unknown molecular mechanisms. Viral replication is induced, resulting in as many as 50,00-200,000 virions per cell. The reactivated virus spreads down peripheral sensory nerve pathways to cutaneous sites, where it may cause a cutaneous outbreak of herpetic lesions. Reactivation of the virus may be asymptomatic.

HSV2 tends to recur more frequently than HSV-1 in the genital area: a median of 5 recurrences per year for the HSV-2 and one for HSV-1 (Benedetti et al, 1999).

NOTES:

1.2 EPIDEMIOLOGY OF GENITAL HERPES INFECTIONS

HSV SEROPREVALENCE IN U.S.

The National Health & Nutrition Survey (NHANES 3, 1988-94) used type-specific antibodies to examine serum samples from over 13,000 Americans to determine the general prevalence of herpes infection in the U.S. population.

- ä Overall HSV2 prevalence rate = 21.9%
- ä HSV2 seroprevalence increases after puberty with the onset of sexual activity
 - <1% prevalence under 15 y
 - 24-28% prevalence over 30 y
- ä HSV2 seroprevalence correlated with: age > 15 y, female sex, Black race or Hispanic ethnicity (15-35% of Caucasians and 35-50% of non-Caucasians are seropositive for HSV-2), lower education, lower income (60% in adults of lower socioeconomic status), marital status, and number of sexual partners. (80% in prostitutes and 3% in nuns).

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INCIDENCE OF CLINICAL DISEASE IN U.S.

It is estimated that 600,00 to 1 million new cases occur each year with 50% of new cases being asymptomatic. Rates of HSV2 infection rose 33% from 1980 - 1990 (Wald).

Genital infections are most often caused by HSV-2 (70-85%), although 10-30% are due to HSV-1.

Genital HSV is diagnosed clinically more often in whites than in non-whites

If HSV2 seroprevalence is higher among nonwhites, why are more infections diagnosed in whites?

- ä Role of viral cross-immunity
 - 70% HSV-1 seroprevalence in blacks vs. 25% in whites
 - Prior infection with HSV-1 attenuates severity of subsequent HSV2 infection (NHANES, 1976-1980).**
 - Therefore, many genital herpes infections may be subclinical in persons with prior oral herpes.
 - Access to health care and health education is higher among whites.

KEY POINTS:

- ä HSV most common overall cause of Genital ulceration in the industrialized world.
- ä In US, most genital herpes caused by HSV-2, but 15-30% caused by HSV-1
- ä Prevalence of HSV-2 infection in US approximates 22%, but most of the infections are subclinical or asymptomatic.

Sexual orientation (AMEN study, 1992): 40% seroprevalence among gay men vs. 20% in heterosexual men. Seroprevalence particularly high in HIV-infected men (68%-77%).

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TRANSMISSION & INCUBATION PERIOD

Transmission is **sexual or vertical** (mother to infant). Viral **inoculation** occurs through **microabrasions** during oral, vaginal or rectal sex with infected partner.

Risk of transmission is difficult to quantify: **10%** of susceptible partners acquired HSV in one year, in a cohort of 144 monogamous heterosexual couples with one HSV2-infected partner (Mertz, 1992). **The majority of new infections were transmitted in the absence of an obvious lesion.** Women were 4x as likely as men to become infected (17% vs. 4%). Prior HSV-1 immunity was partially protective. Condoms were not used regularly in these couples, but did confer some protection in those who used them. A more recent study (Langenberg, 1999) followed 2393 seronegative persons for serologic and clinical evidence of HSV infections. The rates of new acquisition of HSV-1 was 1.6 cases per 100 person-years and HSV-2 was 5.1 cases per 100 person-years. Women were more likely than men to acquire HSV-2, and more likely to have a symptomatic infection. Prior HSV-1 infection did not reduce the rate of HSV-2 infection, but did reduce the likelihood of symptomatic seroconversion.

Although the risk of transmission is proportional to the duration of lesions, most transmissions (70%) occur during asymptomatic periods (Mertz, 1992)

HSV is readily inactivated at room temperature and by drying: **fomite and aerosol transmission unlikely.**

Incubation period for primary is 2-28 days. However, many patients may not experience a primary infection.

1.3 CLINICAL MANIFESTATIONS OF GENITAL HERPES

DEFINITION OF TERMS

1. INITIAL (PRIMARY) INFECTION:

- First infection ever with HSV-1 (15-30%) or HSV-2 (70-85%).

KEY POINTS:

- Prior infection with HSV-1 attenuates severity of subsequent HSV-2 infection.
- Risk of acquiring infection from an infected partner approximates 10% per year
- Most transmission occurs in the absence of clinical lesions.



• **No serum antibody present when symptoms appear.**

• Disease more severe than recurrent disease.

• **Serum antibody rises in convalescence.**

2. INITIAL (NON-PRIMARY) INFECTION

• First symptomatic (clinically apparent) manifestation ever of HSV-1 or HSV-2 in an individual previously seropositive.

• **Serum antibody is present initially but titer rises in convalescence.**

• Homologous type (first clinically apparent HSV2 infection in person with prior HSV2 antibodies OR first clinically apparent HSV-1 infection in person with prior HSV-1 antibodies).

• Heterologous type HSV-2, infection in person with prior HSV1 antibodies OR HSV1 infection in person with prior HSV2 antibodies).

• Manifestations tend to be milder.

3. RECURRENT INFECTION

• Reactivation of latent virus in genital area.

• **Serum antibody is present when symptoms appear and there is generally no change in antibody titer in convalescence.** The patient may or may not be aware of prior outbreaks.

• HSV2 recurs more frequently than HSV-1

• The disease is usually mild and of short duration.

4. ASYMPTOMATIC INFECTION

• **Serum antibody present, no known history of clinical outbreaks.**

• Latently-infected individuals intermittently shed virus without any obvious signs or symptoms in genital area.

NOTES:



5. ASYMPTOMATIC SHEDDING

- ä Approximately $\frac{2}{3}$ of episodes of viral shedding are temporally associated with onset of clinical symptoms (Wald).
- ä $\frac{1}{3}$ of episodes of viral shedding are not associated with any symptoms or signs of disease and go unrecognized (Wald).
- ä reactivation of the virus may be asymptomatic. Up to 20% of persons who are seropositive for HSV-2 are asymptomatic. Another 60% have atypical symptoms, and could be diagnosed, but are not (Wald).
- ä Recent evidence suggests that reactivation of the virus may be asymptomatic. **Up to $\frac{2}{3}$ of persons with positive HSV-2 antibodies have no clinical history of anogenital herpes outbreaks.**

CLINICAL MANIFESTATIONS OF GENITAL HERPES

1. INITIAL (PRIMARY) INFECTION

- ä **Bilateral vesicles** ⇒ pustules ⇒ may coalesce to form a very superficial **painful, non-indurated ulceration** with scalloped edges and erythematous margin (last an average of 11-12 days) ⇒ just as first set of ulcers heals, a second crop erupts in the second week ⇒ crusts ⇒ healed (full re-epithelialization requires an average of 17-20 days). Viral shedding occurs until all the lesions dry up. The median duration of viral shedding (from the onset of lesions to the last positive culture) is about 12 days, and correlates well with the mean time from the onset of vesicles to crusting.
- ä *Bilateral* 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.
- ä *Cervical ulceration* occurs in up to 90% of primary HSV-2 infections and up to 70% of HSV-1 infection. It may manifest itself as mucopurulent cervicitis or may be asymptomatic. The cervix will appear abnormal to inspection in the majority of cases, with ulcerative lesions, erythema, or friability. Clinical differentiation with GC or CT cervicitis may be difficult, although the presence of cervical ulceration suggests herpes. It may be hemorrhagic or frankly necrotic.
- ä Local symptoms are predominantly pain (95%), itching, dysuria (60%), vaginal (85%) or urethral (30%) discharge, and tender inguinal adenopathy (80%).
- ä Severe infection is often associated with constitutional symptoms such as fever, malaise, myalgias, headaches (40% of men and 70% of women). Systemic symptoms peak within 3-4 days of onset of lesions and gradually recede over the next 3-4 days. Visceral involvement, including hepatitis, meningitis or sacral radiculomyelitis with neuralgia,

KEY POINTS: SYMPTOMATIC INITIAL (PRIMARY) INFECTION CHARACTERIZED BY:

- ä Incubation period 2-7 days
- ä Multiple, usually bilateral lesions often accompanied by systemic symptoms
- ä Total duration 2-4 weeks.



urinary retention (10% of women) and obstipation may occur.

2. RECURRENT INFECTION

- ä Recurrences are more likely if the primary episode is prolonged (>30 days)
- ä The prodromal symptoms of localized tingling and irritation occur in about 50% of persons and begin 12 to 24 hours before the appearance of lesions. They can also occur without lesions (“false prodrome”). Painful genital lesions generally last 4 to 6 days, but may last for longer periods. The duration of viral shedding averages 4 days. Lesions tend to be unilateral and localized to a small area.
- ä Cervical involvement is much less frequent than for the initial infection. Cervical viral shedding occurs only in 12 to 20% of women.
- ä 89% of patients with HSV2 have at least 1 recurrence during the first year and 35% had at least 6 recurrences (Benedetti). HSV-2 more prone to recur than HSV-1 (55%) in the first year. The median number of recurrences is 4 for HSV-2 and < 1 for HSV-1. The median number of recurrences is 5 for HSV-2 and 1 for HSV-1.
- ä Recurrences of HSV decrease over time: a decrease of at least two or more recurrences after one year.

3. ATYPICAL PRESENTATIONS AND UNDERDIAGNOSIS

- ä Atypical presentations are common: vulvar erythema, furuncles, vulvar fissures, recurrent balanitis in HIV infected men. One study has demonstrated that characteristic ulcerations of the genital tract were present in only 2/3 of women with positive HSV-2 cultures (Koutsky, 1992).

4. ANORECTAL HSV2

- ä HSV proctitis in homosexuals characterized by: itching, tenesmus (100%), difficulty urinating in 50%, discharge, gray pseudomembranous cryptitis; perianal vesicles occur in 2/3 and are usually found only on anoscopy (Goodell, 1983).
- ä HSV2 can frequently be isolated from anal canal in female infections (Koutsky, 1992).
 - ä more common in primary HSV (36%)
 - ä asymptomatic shedding (43%)
 - ä recurrent infection (11%)
 - ä ONLY site of shedding (31%)

KEY POINTS: RECURRENT OUTBREAKS CHARACTERIZED BY:

- ä Milder symptoms and fewer lesions, usually unilateral and localized
- ä Total duration 5 -10 days
- ä May have atypical appearance, lacking classic vesicular lesions
- ä Average number of recurrences 5/year for HSV-2, < 1 per year for HSV-1.



5. URETHRITIS

- 33% of men with first episodes of HSV have a positive urine culture for HSV. Symptomatic urethritis may cause a clear mucoid discharge.
- Up to 5% of women with the dysuria-frequency syndrome have positive cultures for HSV.

6. ASYMPTOMATIC SHEDDING

- It has been documented in 1% to 25% of seropositive persons (from 0.3 to 4.3% of cultures; frequency estimates seem clearly to depend upon the frequency of sampling).
- A total of 17.6% of 306 women had asymptomatic shedding documented in the year following infection. Rates were highest in the first three months, then declined. Overall, it occurred infrequently in women with established HSV-2 infection (mean 2% of days). It occurred more frequently in women with newly acquired infections (< 2 years; up to 5%-10% of days). According to a recent study, asymptomatic shedding as detected by PCR present in 28% of days (range 0% to 77%).
- Rates of asymptomatic shedding are greater for HSV-2 than HSV-1. However, the presence of serum antibody to HSV-1 seems to decrease rates of asymptomatic shedding with HSV-2.
- Asymptomatic shedding is of slightly briefer duration and lower virus titer than the clinical recurrences. Although it is dramatically reduced by acyclovir chemosuppression, it is not completely eradicated, and is not affected by the treatment of the primary episode with acyclovir.

7. COMPLICATIONS OF GENITAL INFECTIONS

- Aseptic meningitis is more common in primary infections and with HSV-2 than in recurrent infections and with HSV-1. It is more common in women than in men (36% of women with primary HSV-2 infection versus 11% for men). It can be severe, requiring hospitalization and/or parenteral narcotics. Generally, there are no neurologic sequelae. However, a recent paper suggests that meningitis may be recurrent, and that benign recurrent meningitis may be caused by HSV-2.
- Radicular pain and sacral paresthesias (rare).
- Transverse myelitis.
- Autonomic dysfunction (hyperesthesia, neurogenic bladder, constipation and impotence).
- Disseminated (viremic) infection: occasional in patients with atopic eczema, pregnant women, inpatients with impaired cellular mediated immunity and neonates.

KEY POINTS:

- Asymptomatic shedding common with HSV-2 infection
- Can occur up to 28% of days in first two years after infection
- Becomes less frequent with established infection



1.4 LABORATORY DIAGNOSIS

VIRAL CULTURE

- ä The viral culture remains the *gold standard* for diagnosis. It is the most sensitive technique, is highly specific (> 99%), and allows for the easiest typing of virus (1 vs 2). Inoculate specimen into viral transport medium and refrigerate. Stable in transport media for 48-72 hours. Cultures turn positive within 24 to 72 hours, but are generally held for 5 days. **A negative culture does NOT rule out HSV disease.**
- ä **The best yield is obtained from vesicles** (95% vs 70% for ulcers and 30% for crusted lesions), and when the culture is performed early in infection:
 - <7 days in primary HSV
 - <2 days in recurrent HSV
- ä Viral recovery:
 - In initial infection is 55% (+)** from vulva; increased to 77% (+) when swabs are taken from vulva, cervix, and anus (Koutsky, 1992).
 - In recurrence is < 50% (+)** (Koutsky, 1992).

Advantages

Highly specific and allows for typing

Disadvantages

Sensitivity is variable and depends on the age of the lesions

Expensive

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ANTIGEN DETECTION TESTS (DFA OR EIA)

- ä These tests have variable sensitivity (65-85%) compared to culture. They are even less sensitive to detect asymptomatic shedding. They are less expensive than cultures and have a faster turnaround (2-12 hours). False positives may occur.
- ä Can differentiate HSV-1 from HSV-2 using monoclonal antibodies. May be better than cultures for healing lesions.





Advantages

Less expensive than cultures with faster turnaround

Disadvantages

Less sensitive than cultures

Less specific with occurrence of false positive

TZANCK PREP OR PAP

• The Tzanck prep is relatively insensitive (50%), and has a higher yield in primary >>recurrent HSV. It is easy to do in a clinic setting. It is non-specific: cannot distinguish HSV-1 from HSV-2 from VZV.

• Technique:

Scrape the base of a vesicle or ulcer

Fix 95% methanol

Stain with Wright's or Giemsa for 60 seconds

Rinse carefully

Look for multinucleated giant cells

Advantages

Rapid and inexpensive

Disadvantages

Less sensitive and specific than other diagnostic tests

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SEROLOGIC TESTS

Commercially available HSV serologies were not specific until the recent development of new type specific serologic tests. The POckit HSV 2 rapid test by Diagnology can be performed in the office and results can be read on site in less than 10 minutes. Compared to the gold standard of the Western Blot test (available only in research laboratories) specificity to HSV-2 runs between 97-100%, and sensitivity is over 90%. Overall, 70% of primary HSV-2 patients were positive with the POckit within 4 weeks, and 83% within 3 months.

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The other test is the HSV-2 or HSV-1 IgM and IgG ELISA developed by Meridian. It is not a rapid test and needs to be sent out to a commercial laboratory. The sensitivity is lower than the POCKit early in infection (only 8% within 3 months), but otherwise, it has similar test performance characteristics.

There is considerable controversy regarding their general use and no recommendations can be made at this time: however, some experts have suggested the following possible uses

- diagnosing recurrent infection
- detecting nonprimary HSV infection
- detecting asymptomatic shedders who risk transmitting infection to partners
- screening pregnant women

Advantages

POCKit

Rapid, on-site, sensitive and specific

Meridian

Can be used for HSV-1 and HSV-2

Automated

Specific in adults

Disadvantages

POCKit

Only HSV-2

Meridian

Less sensitive early in infection

1.5 TREATMENT

AVAILABLE MEDICATIONS

A. Acyclovir (Zovirax®) (gold standard)

This was the first of a potent new class of antiviral agents, licensed in the 1982. It quickly replaced vidaribine for use in HSV infection. Available in oral, intravenous and topical (latter form generally not recommended because of minimal effectiveness) formulations.

- Works by competing with deoxyguanosine for binding to viral DNA polymerase; no

KEY POINTS:

- Viral culture generally sensitive early in infection/outbreak, but negative culture does not rule out infection
- Older serologic test not specific for HSV-2, so not helpful
- New type-specific serologies (Western Blot, type-specific ELISA) may be useful, for the diagnosis of atypical or subclinical infections



significant affinity for cellular polymerase. Acyclovir uptake and intracellular phosphorylation to the active triphosphate form greatly facilitated by viral thymidine kinase, leading to 40 - 100 fold higher concentrations in HSV-infected cells than in non-infected cells. Terminates viral chain elongation which effectively arrests viral replication.

B. Valacyclovir (Valtrex®)

Parent compound (prodrug) of Acyclovir that is well absorbed and rapidly metabolized to the active form. It has the advantage of a 3-5x higher bioavailability, thus delivering higher levels of active drug with less frequent dosing.

Note: In immunocompromised patients, valacyclovir at doses of 8 grams per day has been occasionally associated with a syndrome resembling hemolytic uremic syndrome or thrombotic thrombocytopenic purpura. However, in doses used for the treatment of genital herpes, valacyclovir appears safe to use in immunocompromised hosts.

C. Famciclovir (Famvir®)

Parent compound (prodrug) of penciclovir, a newer nucleoside analog. Requires phosphorylation with viral thymidine kinase to become active (like acyclovir), so cross-resistance occurs. Famciclovir inhibits the viral thymidine kinase less effectively than acyclovir, but has higher intracellular levels (good oral bioavailability) and a longer half-life (18-20h) than acyclovir, so its efficacy is similar despite less frequent dosing intervals.

D. Foscarnet

A phosphate analogue, it inhibits viral DNA polymerase at the pyrophosphate binding site and has little effect on cellular polymerases. Foscarnet does not require phosphorylation to become active, so it is effective against the TK-negative strains that are resistant to acyclovir, valacyclovir and famciclovir. It is currently licensed for the treatment of CMV infections, but is also used for therapy of acyclovir-resistant HSV and VZV as well.

- ä Parenteral formulation only is available. There are multiple potential toxicities: renal insufficiency, hypocalcemia, hyper/hypophosphatemia, and more rarely neurotoxicity (seizures, peripheral neuropathy) and anemia. Requires administration by infusion pump and serial dose adjustment for alterations in creatinine clearance. Is expensive.

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TREATMENT REGIMENS

In general, factors to be considered in initiating treatment include: severity of symptoms, immune status, pregnancy, history of complications, and cost.

Consult the CDC 1998 Guidelines for Treatment of STDs included in this home study module for full information.



RECOMMENDED TREATMENT OF INITIAL CLINICAL EPISODES

Genital Herpes

Therapy shortens the course of illness by up to 7 days. Dramatic effects especially if medication is taken within 7 days of onset of illness and there is no history of oral HSV. The duration of pain and viral shedding is shortened, and the crusting of lesions occurs more quickly.

Acyclovir 400 mg orally 5 times a day for 7 to 10 days
or
Acyclovir 200 mg orally 5 times a day for 7 to 10 days
or
Famciclovir 250 mg orally 3 times a day x 7-10 days
or
Valacyclovir 1 g orally 2 a day x 7-10 days

Treatment may be extended if healing is incomplete after 10 days of therapy. Dosage may be increased to 400 mg 5 times a day in HIV infected patients (see also subsection 1.7, Genital Herpes and HIV Infection, p. 20)

Rectal Herpes or Stomatitis/Pharyngitis

Consider using higher doses of medication than for genital herpes. Higher doses used in treatment studies, but it is unclear if required.

Acyclovir 400 mg po 5 times daily for 7-10 days

Clinical experience is lacking for effectiveness of famciclovir and valacyclovir in treating proctitis or stomatitis, but they are likely to be effective.



RECOMMENDED TREATMENT OF RECURRENCES

Intermittent therapy for recurrences can shorten the course of viral shedding and accelerates healing. The decision to treat depends on the severity of the outbreak. Treatment appears to have no effect on rate of recurrence or length of interval between outbreaks. There is little benefit if the medication is begun after two days of onset of lesions, so treatment should be started during prodromal period or within one day of onset of lesions.



RECOMMENDED EPISODIC TREATMENT OF RECURRENT INFECTIONS

Acyclovir	400 mg orally three times a day x 5 days
or	
Acyclovir	200 mg orally 5 times a day for 5 days
or	
Acyclovir	800 mg orally twice a day x 5 days
or	
Famciclovir	125 mg orally twice a day x 5 days
or	
Valacyclovir	500 mg orally twice a day x 5 days



RECOMMENDED SUPPRESSIVE THERAPY FOR FREQUENT RECURRENCES (6 OR MORE PER YEAR)

Suppressive therapy has been proven to reduce by 75% to 95% the frequency and severity of recurrent outbreaks. Acyclovir has been used safely for up to 6 years and valacyclovir and famciclovir for up to 1 year. Suppressive therapy has not been associated with the emergence of clinically significant acyclovir resistance among immunocompetent patients.

Acyclovir	400 mg orally twice a day
or	
Famciclovir	250 mg orally twice a day
or	
Valacyclovir	500 mg orally once daily*
or	
Valacyclovir	1000 mg orally once daily

*may be less effective for patients with very frequent recurrences (>10 episodes per year) than other recommended regimens

NOTES:



- ä In order to impact favorably upon the transmission of HSV to uninfected partners, a treatment to reduce asymptomatic shedding is desirable. Studies performed to date, however, give conflicting results as to the efficacy of acyclovir suppression. Both breakthrough viral shedding and transmission of infection have been documented in patients maintained on long-term suppression. Therefore, no recommendations on prevention of transmission regarding suppressive therapy can be made at this time.
- ä After one year of continuous suppressive therapy, discontinuation of therapy should be discussed with the patient to assess the patient's psychological adjustment to genital herpes and rates of recurrences, as the frequency of recurrences tend to diminish over time in many persons.
- ä Insufficient experience with famciclovir and valacyclovir prevents recommendation of these drugs for more than one year.



RECOMMENDED INTRAVENOUS TREATMENT

Intravenous use is reserved for severe primary infections, meningitis, encephalitis, disseminated infection, pneumonitis, hepatitis, and progressive or invasive mucocutaneous HSV.

Acyclovir 5-10 mg/kg body weight IV every 8 hours for 5 to 7 days or until clinical resolution is obtained

After clinical improvement, oral administration of valacyclovir is recommended for a total of 10 days.

1.6 HSV IN PREGNANCY

RISK OF MOTHER TO INFANT TRANSMISSION

The risk of transmission to the infant is highest during delivery when the infant is exposed to infectious secretions in the lower genital tract. However, in utero hematogenous transmission and ascending infection after premature rupture of membranes have also been reported. The factors associated with transmission include: primary infection, viral titer, local immune factors, infant cellular immune function, maternal titers of antibody, and use of fetal scalp monitoring devices.

- ä **The highest risk of transmission occurs in mothers who acquire genital HSV during pregnancy.**

A primary HSV infection acquired during pregnancy has a higher rate of recurrence
 1° episode HSV in mother ⇒ 50% risk of transmission to infant (range 30 - 60%
 depending on study)

- ä **However, the majority (70%) of neonatal HSV infections occurs in infants of women with *no signs or symptoms* of HSV during pregnancy, most of whom (>60%) had no prior history of genital herpes.**

HSV is shed asymptotically in 2.4% of women on the day of delivery.

Asymptomatic shedding during pregnancy does not accurately predict shedding on day of delivery.

The risk of infection in the neonate of a mother with established HSV infection who has HSV shedding at delivery is less than 2%, likely due to the protective effect of maternal antibodies and lower viral titers during recurrences.

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COMPLICATIONS OF NEONATAL HSV INFECTION

Neonatal HSV infection that is acquired intrapartum or postnatally has 3 main manifestations: disseminated infection, CNS infection, and infection limited to the skin, eye and/or mouth. Disseminated infection is a severe disease with a one-year mortality of about 60% (with treatment), and almost 45% of survivors will have neurologic impairment. CNS infection also has a high mortality if untreated, but with treatment is reduced to about 15%; however, up to 60% of survivors will have neurologic damage. Disease limited to skin, mucous membranes and eye has a low mortality, but some children will develop neurologic impairment, possibly due to silent, undetected CNS involvement.

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COMPLICATIONS OF HSV IN PREGNANT WOMEN

Disseminated HSV can occur rarely, especially in the third trimester.

Systemic disease with visceral involvement including hepatitis, pneumonitis and coagulopathy.

Treatment with intravenous Acyclovir is indicated, though the effects on the fetus are uncertain.

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MANAGEMENT OF HSV DURING PREGNANCY

Prior to 1988, the American College of Obstetrics & Gynecology (ACOG) recommended performing weekly viral cultures during pregnancy in women with known genital herpes, and recommended Cesarean section for any positive surveillance culture.

However, surveillance cultures were not predictive of shedding at time of delivery and resulted in excessive numbers of Cesarean sections, so are no longer recommended.

Current clinical strategies focus on women with known HSV infection, either primary or recurrent disease. **Current ACOG guidelines recommend:**

A. Primary HSV

- ā Antiviral therapy for primary infection is recommended to reduce viral shedding and enhance lesion healing. Suppressive therapy should be considered to reduce the potential of continued viral shedding and the likelihood of recurrent episodes. In one randomized study, acyclovir suppression after 36 weeks of pregnancy reduced the number of cesarean sections at delivery, but due to the small sample size of the study, no reduction in infection rate was demonstrated (no infections in either group).
- ā Although acyclovir (a class C medication) is not FDA-approved for use in pregnancy, numerous studies have demonstrated its safety during pregnancy, and the CDC-maintained acyclovir pregnancy registry has failed to show any increase in fetal anomalies in women who received acyclovir during the first trimester of pregnancy. The newer medications, valacyclovir and famciclovir, are both class B medications, but like acyclovir, neither is FDA-approved for use in pregnancy.
- ā **Women should be carefully inspected for lesions immediately prior to delivery and Cesarean section should be performed for any woman with typical prodromal symptoms or lesions consistent with HSV.** Cesarean section, if performed within 4 - 6 hours of membrane rupture, has been shown to reduce the risk of infection in neonates of mothers with primary HSV infection.

B. Recurrent HSV

- ā **Women should be carefully inspected for lesions immediately prior to delivery and Cesarean section should be performed for any woman with typical prodromal symptoms or lesions consistent with HSV.** Although Cesarean section reduces the transmission rate in cases of primary HSV infection, it is unclear if the same is true for cases of recurrent outbreaks, where the risk of

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transmission is much lower. However, due to the serious nature of the disease if transmission occurs, the ACOG guidelines still recommends cesarean section for those with active lesions at delivery.

- ä A randomized trial of acyclovir given after 36 weeks of pregnancy in women with history of recurrent genital herpes demonstrated a significant reduction in clinical recurrences and a trend towards fewer cesarean sections, but no infections occurred among infants in either group. It is not clear yet if such a practice is beneficial and cost-effective.

C. Asymptomatic Shedding of HSV

- ä Although this group accounts for the largest number of neonatal cases, there is to date no rapid method for detecting HSV in asymptomatic females. None of the current rapid Antibody (DFA, EIA) tests are reliable; and Polymerase Chain Reaction (PCR), although available, has not been adapted for clinical use. More research is needed to identify the factors which promote HSV transmission in asymptomatic shedders, in order to intervene effectively in this group. No recommendations can be made at the present time.

D. Management of Exposed Newborn

- ä Infants exposed to HSV at birth (proven by virus isolation or presumed by observation of lesions) should be followed carefully. Some authorities recommend that such infants undergo surveillance cultures of mucosal surfaces to detect HSV infection prior to the development of clinical signs, but others argue that the low risk of transmission (in non-primary cases) and the expense of such surveillance cultures makes such a practice unfeasible. Routine administration of acyclovir is not currently recommended by experts, unless the mother acquired herpes near term, when the risk of infecting the fetus is highest.

E. Prevention

- ä Prevention of neonatal HSV must center on preventing HSV acquisition in late pregnancy.

1.7 GENITAL HERPES AND HIV INFECTION

EFFECT OF HSV ON HIV

A. HSV has been shown to facilitate HIV Transmission

- ä 78% of HIV (+) women presenting to Baltimore STD clinic were also HSV2 (+) vs. 58% HIV (-) women (Hook, 1992)

KEY POINTS:

- ä Risk of transmission is highest for primary maternal infection (30-60%), and is much lower for recurrences (< 2%)
- ä Most cases occur in infants or women without signs or symptoms of HSV infection during pregnancy
- ä Cesarean section is indicated if active lesions are present at the time of delivery
- ä Acyclovir suppression may be useful for cases of primary infection during pregnancy

- ä 80% of gay male HIV-seroconvertors in San Francisco were HSV2 (+) vs. 46% of HIV (-) (Holmberg, 1988)

B. Genital Ulcer Disease (GUD) has been associated in several good epidemiologic studies with increased risk of acquiring HIV infection (Odds ratio = 8x)

- ä Genital herpes associated with 1.5x increased risk acquiring HIV
- ä Higher HIV viral load has been detected in herpetic ulcers (Schacker, T. 1997)

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EFFECT OF HIV INFECTION ON GENITAL HSV

A. HIV infection increases severity and duration of genital HSV

- ä Large, slow-healing ulcers of >1 month's duration
- ä ↑ risk of disseminated primary infection
- ä Episodes of recurrent HSV becomes more frequent and severe as ↓ CD4 < 350
- ä Atypical lesions are common : erythema, epidermal cracks, deep fissuring
- ä HSV proctitis occurs esp. among gay men, with anorectal pain, diffuse rectal ulceration, sacral paresthesias, difficulty voiding
- ä AIDS case definition if lesions persist > 1 month

B. Frequency of asymptomatic shedding increases

- ä 75 - 80% of HIV+ with HSV-2 infection have detectable shedding over a month of follow-up
- ä Virus cultured on 10% of days
- ä 2/3 of the reactivations were subclinical.

C. Acyclovir resistance occurs

- ä In HIV (+) patients with CD4 counts <50
- ä Associated with use of acyclovir for suppression
- ä Possible mechanisms described: reduction or absence of thymidine kinase (TK) synthesis

NOTES:

- alterations in substrate specificity of TK, or alterations in substrate specificity of DNA polymerase.
- ä Evoked by selection of mutant viruses that are thymidine-kinase deficient.
 - ä May respond to therapy with Foscarnet, a pyrophosphate analogue, that directly inhibits viral DNA polymerase.
 - ä All acyclovir resistant strains are resistant to valacyclovir, and most are resistant to famciclovir.

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MANAGEMENT OF GENITAL HERPES IN HIV INFECTION

Treatment should be instituted immediately on the basis of clinical suspicion, without waiting for viral culture confirmation, because of the potential for dissemination of infection. There may be benefit to using increased dosages of antiviral drugs. Regimens such as acyclovir 400 mg po 3 to 5 times daily, as used for other immunocompromised persons, has been found useful. Famciclovir 500 mg twice a day has been shown effective in decreasing the rates of recurrences and of subclinical shedding in HIV infected persons. For treatment of acyclovir resistant genital herpes, foscarnet 40 mg/kg body weight IV every 8 hours until clinical resolution is attained is often effective. Topical cidofovir gel 1% applied to the lesion once daily for 5 consecutive days also appears effective in many patients.

The management of subclinical infections in HIV-infected patients is controversial. Subclinical reactivations have been shown to increase the HIV RNA levels in those whose viral loads are not suppressed by medication. Whereas some studies from the late 1980's and early 1990's demonstrated a survival benefit for those on chronic acyclovir suppression, no similar data is available since potent antiretroviral combination therapy has become widely utilized, so no recommendations for or against antiherpetic suppressive therapy can be made.

CONTACTS

Discuss the treatment history of disease with emphasis on potential for recurrent episodes, asymptomatic viral shedding and sexual transmission. **Advise to abstain from sexual activity when lesions or prodromal symptoms are present and encourage to inform partners that they have HSV.** Use of condom should be encouraged during all sexual exposure with new or uninfected sex partners.

Transmission can occur without lesions and most cases are transmitted during asymptomatic periods. Asymptomatic shedding is more common with HSV-2 than HSV-1 and with those with genital HSV infection of less than 12 months duration.

NOTES:

Risk of neonatal infection should be explained to all patients, including men. Women of reproductive age should be advised to inform health care providers during pregnancy about their HSV.

Advise patient with first episode HSV that episodic antiviral therapy may shorten duration of symptoms and suppressive therapy can prevent recurrence but not viral shedding. Whether episodic or suppressive therapy prevents sexual transmission is currently unknown.

1.9 PREVENTION OF HSV

Barrier contraception for anogenital HSV - probably necessary for all sexual encounters in infected patients.

Sex partner are likely to benefit from evaluation and counseling.

Since condoms are not 100% effective susceptible pregnant women whose partners have known oral or genital HSV or those sex partners' infection status is unknown, should be counseled to avoid unprotected genital and oral sexual contact in late pregnancy to prevent neonatal HSV which is associated with initial maternal infection near the time of delivery.

Reduce events that trigger recurrences (e.g. stress).

1.10 REVIEW QUESTIONS

1. A 27 year old female comes to your office requesting suppressive therapy for HSV. She was diagnosed with the disease about 2 years ago. She states she has about six episodes of recurrent infections a year. She does not have a regular sexual partner. How would you manage this patient?

2. One of your patients, a 30 year old HIV infected man, presents to the clinic complaining of recurrent episodes of anal pain and burning. He is on antiretroviral therapy. His latest CD4 count was 300. Upon examination, there are multiple fissures in the anal area with some erythema. How would you manage this patient?

3. A 26 year old patient is diagnosed with primary herpes. Her partner of six months is asymptomatic, and she wonders how she may have gotten the infection. She is worried about future pregnancies. How would you manage her partner and how would you counsel her about transmission?

4. Answer the question that appears on the video tape for HSV.

A) _____

B) _____

C) _____

5. Answer the question that appears on the video tape for HSV.

A) _____

B) _____

6. Answer the question that appears on the video tape for HSV.

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