# GENITAL HERPES SIMPLEX VIRUS (HSV) INFECTIONS

**This chapter from the Canadian Guidelines on Sexually Transmitted Infections 2006 Edition has undergone revisions and has been updated as of October 2007. The chart below summarizes the most significant changes made to the chapter and cross-references the corresponding page numbers in the current hard copy version of the guidelines.**

| Section | Page | Current Wording/Problem | Update/Clarification |
|---|---|---|---|
| **Treatment** ***Table 3*** | **151** | Footnote under Table 3 related to use of famciclovir assuppressive therapy<br><br>Safety and efficacy data suggest that acyclovir and valacyclovir can be administered up to 1 year [A- I] based on controlled trials47–59,62<br><br>whereas famciclovir has been evaluated only for up to 4 months' [A-I] administration.60,61 | Changed wording to:<br>Based on controlled trials, safety and efficacy data suggest that acyclovir,valacyclovir and famiciclovir can be administered for up to 1 year [A-I] 47-62 |
| **Treatment** ***Table 3*** | | Suppressive therapy during pregnancy has been updated.<br><br>Acyclovir 200 mg qid [A-I] 63,64<br>OR 400 mg tid [A-I] 65,66<br>Both regimens have been evaluated and shown to be efficacious in reducing recurrent disease and the need for Cesarean section.<br>Both regimens require initiation of suppression with acyclovir 400 mg tid at 36 weeks with termination at parturition [A-I] 65,66 | Changed to:<br><br>Acyclovir 200 mg PO qid [A-I] 63,64<br>OR<br>Acyclovir 400 mg PO tid [A-I] 65,66<br>OR<br>Valacyclovir 500 mg PO bid [A-I] 67<br>All regimens have been evaluated and<br>shown to be efficacious in reducing recurrent disease and the need for Cesarean section.<br>All regimens require initiation of suppression at 36 weeks with termination at parturition [A-I] 63-67 |

# GENITAL HERPES SIMPLEX VIRUS (HSV) INFECTIONS

## Etiology

- Herpes simplex virus (HSV) types 1 and 2.[1]

## Epidemiology

- The annual incidence in Canada of genital herpes due to HSV-1 and -2 infection is not known (for a review of HSV-1/HSV-2 prevalence and incidence studies worldwide, see Smith and Robinson 2002[2]). In the United States, it is estimated that about 1,640,000 HSV-2 seroconversions occur yearly (730,000 men and 910,000 women, or 8.4 per 1,000 persons).[3]
- Based on the change in prevalence of the serum antibody to HSV-2, HSV-2 increased 30% between 1976 and 1994, from 16.4-21.9% in Americans aged 12 years and older.[4]
- In British Columbia in 1999, the seroprevalence of HSV-2 antibody in leftover serum submitted for antenatal testing revealed a prevalence of 17.3%, ranging from 7.1% in women 15-19 years old to 28.2% in those 40-44 years.[5]
- In attendees at an Alberta sexually transmitted infection (STI) clinic in 1994 and 1995, the seroprevalence of HSV-1 and -2 in leftover sera was 56% and 19%, respectively.[6]
- The incidence and prevalence of HSV-1 genital infection is increasing globally, with marked variation between countries.[7]
- In Norway, a recent study found that 90% of genital initial infections were due to HSV-1.[8]
- In Nova Scotia, 58.1% of 1,790 HSV isolates from genital lesion cultures in women were HSV-1; in men, 36.7% of 468 isolates were HSV-1.[9]
- Females are at higher risk of acquiring genital herpes from a male partner than males are from a female partner. Studies have found that among discordant heterosexual couples with a source partner who had symptomatic recurrent genital HSV-2 infection, the annual transmission rates were 11-17% in couples with male source partners and 3- 4% in couples with female source partners.[10,11]
- In one study, transmission in 70% of patients appeared to result from sexual contact during periods of asymptomatic virus shedding.[11]
- Pre-existing seropositivity to HSV-1 reduced the likelihood of acquiring symptomatic genital HSV-2 disease in women by 55-74%,[11,12] although others have not observed such a protective effect.[10,13]

## Natural history

- The incubation period averages 6 days.[1]
- Of new HSV-2 infections diagnosed by seroconversion, approximately 60% are asymptomatic and 40% symptomatic. Of the symptomatic cohort, about 80% present with typical genital symptoms and signs, while 20% have atypical presentations, including nonlesional HSV-2 infections such as genital pain or urethritis, aseptic meningitis and cervicitis, which are well-recognized complications of first episodes of genital HSV infection.[1]

- No intervention, including early initiation of antiviral therapy, prevents the development of latent sacral sensory ganglion infection.[14]
- Recurrences tend to occur in tissues innervated by sacral sensory nerves.
- Recurrences may be preceded by warning signs (prodromal symptoms) a few minutes to several days before lesions appear, such as focal burning, itching (most common), tingling or vague discomfort.[15]
- Recurrences may be associated with the menstrual cycle, emotional stress, illness (especially with fever), sexual intercourse, surgery and certain medication — so-called "trigger factors."[15]
- Initial mean recurrence rates are greater in persons with genital HSV-2 infection than in those with HSV-1: 4% and 1% per year, respectively, with marked interindividual variation.[16]
- The average recurrence rate decreases over time by around 0.8 outbreaks per year, every year (no matter how high the initial outbreak rate was). However, approximately 25% of patients reported more recurrences in year 5 than year 1, evidence again of the substantial interindividual differences in recurrence rates.[17]
- Asymptomatic shedding of HSV can be demonstrated by virus identification through culture or polymerase chain reaction (PCR). HSV DNA can be detected four to five times more frequently by PCR than by culture.[18,19] However, identification of virus by PCR may not be synonymous with infectivity. The following data pertain to shedding demonstrated by isolation of infectious virus:
  - Asymptomatic shedding prevalence is greater in women with HSV-2 genital infection than with HSV-1 (55% vs 29% during a median follow-up of 105 days).[18] A similar difference may exist in men.[19]
  - Asymptomatic shedding of HSV-2 is as common in persons with symptomatic genital infection (while in between outbreaks) as in those with asymptomatic genital infection.[18–20]
  - Asymptomatic shedding occurs on an average of 2% of days for a mean duration of 1.5 days.[18,19] HSV has been isolated from vulva, cervicovaginal and rectal sites in women[20] and from penile and perianal skin, urethra and urine in men.[19]

**Prevention**

- Patients presenting with concerns about STIs and/or prevention of pregnancy provide clinicians with an important opportunity for instruction and encouragement about consistent safer-sex practices. Given the increase in HSV-1 genital infection, likely due to orogenital sex (perhaps as an alterative to genital intercourse), patients need also to be advised of the inherent risk of genital herpes from such an activity.[21]
- At the time of diagnosis of an STI, review and monitor prevention practices.
- Identify barriers to prevention and the means to overcome them.
- Condom use reduces transmission of genital HSV-2 from infected men to women by 50% and may reduce transmission from infected women to men to a similar degree.[22] However, condom effectiveness is greatly limited by non-use and may also be limited because of the location of lesions and the risk of transmission during orogenital sex. Other safer-sex practices should be discussed.

- Valacyclovir 500 mg ingested daily by a patient with genital HSV-2 infection has been shown to reduce transmission to a susceptible heterosexual partner by 48%. The effect of condoms and suppressive valacyclovir may be additive.[10]
- Immunization with a glycoprotein D–adjuvanted vaccine has been demonstrated to protect against acquisition of genital HSV disease in women who were seronegative for both HSV-1 and -2, but not for those who were seropositive for HSV-1.[23] It had no protective efficacy in men, regardless of serostatus. Protection against genital HSV disease was 74%, and protection against infection (seroconversion plus symptomatic infection) was 46%. Practitioners should be aware that such a vaccine may become available for use in the next 5-10 years.

**Manifestations**

- A diagnostic lesion is a cluster of vesicles on an erythematous background.

***Initial symptomatic episodes***

- Primary
  - First clinically evident episode in an HSV-antibody–negative individual.
  - Five characteristics:[1]
    - Extensive painful vesiculoulcerative genital lesions, including exocervix.
    - Systemic symptoms in 58-62% (fever, myalgia).
    - Tender lymphadenopathy in 80%.
    - Complications: 16-26% develop aseptic meningitis, and 10-28% develop extragenital lesions.
    - Protracted course: mean 16.5 (men) to 22.7 (women) days to resolve.
- Non-primary[1]
  - First clinically evident episode in a person who, by testing, is demonstrated to have pre-existing heterologous antibody. Generally the range and severity of symptoms and signs of even the most severe cases are less marked than in those with severe primary infection. This has been attributed to a mitigating effect of pre-existing heterologous immunity in attenuating the severity of disease.
  - Compared to primary genital herpes, non-primary infections are characterized by the following:
    - Less extensive genital lesions.
    - Systemic symptoms in only 16%.
    - Complications uncommon: meningitis in 1% and extragenital lesions in 8%.
    - Duration less prolonged: mean 15.5 days.

### *Recurrent disease*[1,24]

- The first clinically evident episode in a person with pre-existing homologous antibody (i.e. culture of HSV-2 from a first outbreak in an individual with demonstrable HSV-2 antibody) may sometimes be confused with a primary infection.[24] This is because overlap occurs in the frequency of local symptoms, fever and size of genital lesions between those with recently acquired genital herpes and those, who, by serologic testing, are determined to have acquired infection remotely but are now experiencing a first outbreak.[24]
- In one study, almost 10% of patients judged to have a first-episode of genital herpes had serologic evidence of remotely acquired HSV-2 infection, indicating that clinical differentiation of primary genital infection and previously acquired infection can be difficult.
- Thus, typing of the virus isolate and type-specific serologic testing are required to differentiate between the two entities: primary/non-primary infection vs. a first lesion due to reactivation of a (long) latent infection acquired previously (see Diagnosis section, below).

### *Characteristics of recurrent disease*

- Due to reactivation of latent sacral sensory ganglion infection.
- Typically, localized small painful genital lesions (mean lesion area 10% of that in primary genital herpes).[1]
- Systemic symptoms in 5-12%.
- Prodromal symptoms in 43-53%, for an average of 1.2-1.5 days.
- Mean duration of lesion 9.3-10.6 days.

### *Asymptomatic shedding*

- See Natural history section, above.

## Diagnosis

### *Specimen collection and laboratory diagnosis*

- Culture is the most common method currently used in public health laboratories in Canada to confirm the clinical diagnosis of HSV. It is sensitive (70% from ulcers, 94% from vesicles) and permits identification of HSV type.[25]
- PCR is four times more sensitive than HSV culture and is 100% specific.[26] However, at this time, PCR assays have not yet replaced culture for routine diagnosis of genital herpes in public health laboratories in Canada.
- The Tzanck smear demonstrating diagnostic multinucleated giant cell is 40-68% as sensitive as culture, while direct fluorescent antibody has a sensitivity of 56% compared to culture.[25,27] Neither test can thus be relied on for laboratory confirmation of diagnosis.
- The antibody response to primary infection is characterized by early appearance of IgM, followed subsequently by IgG antibody. IgM antibody usually wanes within a few months of infection;[28] therefore, the presence of IgM antibody is an indirect indication of “recent” infection.

- A primary infection is confirmed by demonstrating an absence of HSV antibody in the acute-phase sample and the presence of antibody in the convalescent blood sample (i.e., seroconversion).
- Most individuals seroconvert within 3-6 weeks; by 12 weeks, more than 70% will have seroconverted.[29,30]
- The advent of testing for type-specific antibody will allow practitioners to establish a diagnosis of primary infection and determine whether the infection is due to HSV-1 or -2. Such information will also permit practitioners to counsel individuals with genital herpes and their partners. Type-specific antibody is best detected by Western blot analysis, although new commercial enzyme immunoassays with improved sensitivity and specificity are available.[31] Enzyme immunoassay test results need not be routinely confirmed by Western blot analysis. At this time, type-specific HSV antibody assays are available only in a few laboratories in Canada (see Special Considerations section, below).
- During recurrent genital HSV infection, no consistent HSV antibody changes occur. Specifically, IgM appears inconsistently, and IgM titres also do not change between acute and convalescent samples.[32]
- Detection of HSV-2 antibody is considered to be accurate for detecting silent genital HSV-2 infection, but detecting HSV-1 antibody is not useful in the same way, because asymptomatic HSV-1 orolabial infection is common.[31]

**Management**

- Counselling is an important component in management. Genital HSV infection is not curable, but its somatic and psychological morbidity can be ameliorated by sensitive, empathetic, knowledgeable counselling. Thus, all patients who have genital HSV infections and their sexual partner(s) can likely benefit from learning about the chronic aspects of the disease after the acute illness subsides. Explain the natural history of the disease, with emphasis on the potential for recurrent episodes, asymptomatic shedding and sexual transmission. Advise patients that antiviral therapy for recurrent episodes may shorten the duration of lesions, and suppressive antiviral therapy can ameliorate or prevent recurrent outbreaks, with one drug having been demonstrated to reduce transmission.[10]
- The most common psychological patient concerns include the following:
  - Fear of transmission.
  - Fear of being judged or rejected by partner.
  - Loneliness, depression and low self-esteem.
  - Anxiety concerning potential effect on childbearing.
- Patients need to inform their sex partner(s) that they have genital herpes. It may be useful to have the partner receive counselling concurrently for information and possible serologic testing for HSV-1 and/or -2 antibody.
- Type-specific serologic testing for HSV-1 and/or -2 antibody can demonstrate whether couples are discordant or concordant for HSV-1 and/or -2 infection. Such information will be useful in counselling couples about the risk of transmission of genital herpes infection.
- It should be emphasized that most transmission of genital herpes occurs in the context of asymptomatic shedding.[11] Therefore, emphasizing the use of condoms and suppressive antiviral drug therapy is important for reducing the risk of transmission.
- Transmission of genital herpes is decreased by the following:

  - Avoidance of contacts with lesions during obvious periods of viral shedding (prodrome to re-epithelialization) from lesions. Advise patients that they should abstain from sexual activity from the onset of prodromal symptoms until the lesions have completely healed.
  - Condom use (see Prevention section, above).[22]
  - Daily suppressive antiviral therapy, which reduces recurrent lesions, asymptomatic viral shedding and transmission.[10]
- Assess patients with genital herpes for other STIs and treat as needed.[33]
- Discuss the risk of neonatal infection with all patients, including men. Women who have genital herpes should be advised to inform the health care providers who care for them during pregnancy about their HSV infection.
- Genital herpes increases the risk of acquisition of HIV twofold.[34]

## Treatment[35]

### *First episode*

- Treatment is recommended for clinically important symptoms.
- Analgesia and laxatives may be required. Urinary retention may be an indication for hospitalization.

***Table 1. Treatment for first episode***

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|---|
| • For severe primary disease, IV acyclovir 5 mg/per kg infused over 60 minutes every 8 hours *[A-I]* is optimal, with conversion to oral therapy when substantial improvement has occurred.[36] |
| • Acyclovir 200 mg PO five times per day for 5-10 days *[A-I]* [37]<br>OR<br>• Famciclovir 250 mg PO tid for 5 days *[A-I]* [38,39]<br>OR<br>• Valacyclovir 1000 mg PO bid for 10 days *[A-I]*[40] |
| • Acyclovir 400 mg PO tid for 7-10 days is recommended by the U.S. Centers for Disease Control *[A-III]*[24] |

**Notes:**

- Oral acyclovir, famciclovir and valacyclovir are comparably efficacious.
- Acyclovir has been initiated as late as 5-7 days after onset of symptoms with benefit[37]; famciclovir has been initiated only in patients with symptoms of fewer than 5 days' duration and valacyclovir in those with fewer than 72 hours of symptoms.
- Topical acyclovir does not alleviate systemic symptoms and should not be used.[37]

### *Recurrent lesions*[35]

***Table 2. Treatment for recurrent episodes***

- Valacyclovir 500 mg PO bid OR 1 g PO qd for 3 days *[B-I]*[41]

OR

- Famciclovir 125 mg PO bid for 5 days *[B-I]*[42]

OR

- Acyclovir 200 mg PO 5 times/day for 5 days *[C-I]*[43]

- A shorter course of acyclovir 800 mg PO tid for 2 days appears as efficacious as the approved 5-day regimen *[B-I]*[44]

**Notes:**

- Valacyclovir, famciclovir and acyclovir are approved for treatment of recurrent genital herpes lesions.
- To be effective, these drugs need to be started as early as possible during the development of a recurrent lesion — preferably fewer than 6 hours (famciclovir) to 12 hours (valacyclovir)after the first symptoms appear. Patient-initiated therapy at the onset of prodromal symptoms has been proven effective in a Canadian study.[42] To achieve this end, patients should have medication on hand and be provided with specific information on when to initiate therapy.

### *Suppressive therapy*[35]

- Suppressive therapy is intended for patients with frequently recurring genital herpes, generally for those with recurrences at least every 2 months or 6 times per year. In such patients, suppressive therapy is preferred to episode therapy[45] and improves quality of life.[46]
- For individuals with fewer than 6 recurrences per year or one every 2 months, episode therapy is recommended (see above). However, suppressive therapy will probably be efficacious and may be considered on a case-by-case basis.

***Table 3. Suppressive therapy for non pregnant patients***

- Acyclovir 200 mg PO three to five times daily OR 400 mg PO bid *[A-I]*[47–59]

OR

- Famciclovir 250 mg PO bid *[A-I]*[60,61]

OR

- Valacyclovir 500 mg PO qd *[A-I]* (for patients with nine or fewer recurrences per year) OR 1000 mg qd *[A-I]*[57,62] (for patients with more than nine recurrences per year)

**Notes:**

- Acyclovir, famciclovir and valacyclovir are approved for suppressive therapy in Canada.
- Based on controlled trials, safety and efficacy data suggest that acyclovir, valacyclovir and famciclovir can be administered for up to 1 year. [47–62]

***Table 4. Suppressive therapy for pregnant patients***

- Acyclovir 200 mg PO qid *[A-I]* [63,64]

OR

- Acyclovir 400 mg PO tid *[A-I]*[65,66]

OR

- Valacyclovir 500 mg PO bid *[A-I]*[67]
- All regimens have been evaluated and shown to be efficacious in reducing recurrent disease and the need for cesarean section.
- All regimens require initiation at 36 weeks with termination at parturition *[A-I]* [63-67].

**Notes:**

- There have been no studies of sufficient power to adequately assess whether suppressive antiviral drug therapy in pregnancy reduces maternal-to-child transmission or neonatal herpes *per se*.
- Suppressive acyclovir and suppressive valacyclovir have been demonstrated to reduce recurrence rates, as well as asymptomatic shedding, and thereby obviate the need for cesarean section to prevent neonatal herpes.[63–67]
- Use of acyclovir suppression does not eliminate the need to observe the neonate carefully for possible HSV infection.
- Acyclovir & valacyclovir safety has been evaluated in limited numbers of pregnant women in controlled trials and these trials concluded that acyclovir and valacyclovir treatment during pregnancy were not harmful to the fetus and did not result in any significant increase in adverse events.[63,65,67] Data from 1207 women reported to the Acyclovir Pregnancy Registry including results from 111 women treated with valacyclovir support the conclusions of these controlled trials. [68]

***Table 5. Therapy for neonatal herpes***

- Acyclovir 45–60 mg/kg/day IV in three equal 8-hourly infusions, each over 60 minutes for 14 to 21 days *[A-I]*.[69]

**Note:**

Consultation with a colleague experienced in this area should be sought.

## Consideration for Other STIs

- Having HSV can increase the risk of acquiring and transmitting HIV. This increased risk needs to be explained; HIV testing with pre- and post-test counselling should be offered.
- Genital ulcers can also be caused by syphilis, chancroid or lymphogranuloma venereum, and testing for these should be considered.
- Testing for other STIs, including chlamydia and gonorrhea, should be considered.
- Immunization for hepatitis B may be indicated.
- See *Primary Care and Sexually Transmitted Infections* chapter.
- Discuss HPV vaccine with women as per the recommendations outlined in the Canada Communicable Disease Report, Volume 33 ACS-2, (2007) *National Advisory Committee on Immunization (NACI) statement on Human papillomavirus vaccine.*

## Reporting and partner notification

- At the time of publication, genital HSV infections were reportable by physicians to local public health authorities in New Brunswick, Nova Scotia, Prince Edward Island and Newfoundland. Neonatal HSV infections are reportable in some provinces only. Whether cases are to be reported on suspicion or after laboratory confirmation also varies.
- Partner notification is not required as a public health measure, in part because of the following:
  - Most disease presents as recurrences.
  - It is difficult to assess whether a contact has ever had a primary genital infection.
  - Patients with genital herpes should be encouraged to inform their sexual partner(s) from the preceeding 60 days prior to symptom onset or date of diagnosis where asymptomatic to make them aware of the risk of infection, if uninfected, and to aid diagnosis in a partner if the disease does arise.

## Follow-up

- Follow-up cultures are not indicated, except when there are unusual recurrent symptoms or to determine in vitro susceptibility when resistance is suspected as a cause of therapeutic failure.
- Supportive counselling is an important component of managing patients with genital herpes.

## Special Considerations

### *Neonatal herpes*[70,71]

- Recent epidemiologic work on risk factors for neonatal herpes[70] has demonstrated that the greatest risk factor for neonatal HSV infection is new maternal genital HSV-1 or -2 infection without a fully developed maternal immune response by the time of delivery, resulting in an infant born without homologous transplacental HSV type-specific antibody. Four of nine such infants developed neonatal HSV infection. On the other hand, infants delivered vaginally by women with reactivation of genital herpes with genital lesions or asymptomatic HSV genital virus shedding at parturition had a 2% risk of infection (2 of 92 cases). Cesarean delivery was shown definitively to protect against neonatal transmission of HSV. Thus, the opportunity for preventing neonatal HSV relates more to obviating maternal genital infection late in pregnancy than to identifying women with known genital HSV infection. That is, there is reason for reassurance of pregnant women with a history of genital herpes.
- Incidence in Canada for 2000-2003 inclusive is 5.85 per 100,000 live births; 62.5% of these infections were attributed to HSV-1.[72] From 55-80% are due to HSV-2.[73–76]
- Intrauterine infection accounts for 5% of neonatal HSV infection, and postnatal infection (usually HSV-1) for 15%.[74–76]
- Clinically, neonatal infection is classified as skin-eye-mouth (SEM), central nervous system (CNS) or disseminated infection. Mortality is 0%, 15% and 47%, respectively, and abnormal development at 1 year is 2%, 70% and 25%, respectively.[73,74,76] However, overlap occurs, and up to 30% of babies with SEM initially will progress to CNS disease as well.

- In the Canadian study, 63.8% of cases had localized (SEM) disease, while 34.5% had infection that disseminated to the CNS or other organs.[72]
- Vesicular skin lesions may not be observed in 17% with SEM, 32% with CNS and 39% of neonates with disseminated disease.
- Risk of neonatal infection:
  - Is up to 50% if mother has primary genital HSV infection with lesions at parturition.[75] In approximately 70% of cases the mother has no history of genital herpes.[74,76]
  - Is from 2-8% when vaginal delivery occurs and mother has a recurrent genital lesion or has asymptomatic genital HSV shedding at parturition.[70,77]
- Median incubation period is 4 days, with a range of 1-28 days.[73,74,76]
- Most neonatal herpes begins after a seemingly healthy neonate has left hospital.
- Acyclovir oral therapy suppresses recurrent genital disease and asymptomatic shedding and thereby has been shown to reduce the need for cesarean delivery (see Treatment section, above).

***Laboratories offering HSV type-specific serum antibody testing***

- Alberta Provincial Laboratory for Public Health, Edmonton, Alberta (implementation anticipated in 2005).
- National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, Manitoba.
- Regional Virology & Chlamydia Laboratory, Hamilton, Ontario.
- Children's Hospital of Eastern Ontario Laboratory, Ottawa, Ontario.
- Warnex Inc., Montreal, Quebec.

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