Chapter 2
Genital Herpes

D. Gene Parks

Introduction

Herpes simplex virus (HSV) has a long and confusing history. More than 2,500 years ago, Hippocrates first used the word "herpes," derived from the Greek word "to creep," to describe how the lesions of this contagious ulcerative disease seemed to creep or crawl along the skin [1]. Galen first noted that recurrences develop at the same anatomic site. However, over time, the word herpes was used to describe many skin conditions from lupus to zoster. The definition of herpes (particularly oral lesions) became more rigorous in the seventeenth century. In the 1830s, recurrent genital herpes was described and 60 years later was identified as a "vocational disease"—a sexually transmitted infection (STI). The virus itself was not identified until the 1950s. In 1971, it was proposed that two different types of HSV caused infection. HSV-1 commonly causes labial or pharyngeal infection, and transmission is primary by nongenital contact. HSV-2 typically affects the genital area and is transmitted by intimate sexual contact. However, both viruses are capable of causing either genital or oral-pharyngeal infections that appear identical on examination. In the United States, HSV infection is one of the most common STIs and is the leading cause of genital ulcers.

Fast Facts

- Genital herpes is one of the most prevalent STIs in the United States. About 50 million Americans have genital HSV infection.

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- HSV is the leading cause of genital ulcers. HSV-2 infections at least doubles the risk of sexual acquisition of human immunodeficiency virus (HIV) and also increases transmission.
- Herpes is a chronic, lifelong infection; patients can shed virus, not only during outbreaks but also during asymptomatic periods.
- Intrapartum transmission of HSV-2 can cause neonatal death or permanent neurological damage.
- Testing for HSV-2 antibodies is not recommended for general population screening.

Prevalence and Incidence

The full extent of the HSV epidemic in the United States is not known because (1) HSV infection is not a reportable disease in most states, (2) most people carrying the virus are not aware that they are infected, and (3) it is not possible in many cases for people to distinguish between an initial outbreak (incidence) and a recurrence (prevalence).

Serology studies suggest that 50 million people in the United States have genital HSV infection. In Europe, HSV-2 is found in 8–15 % of the general population. In Africa, the prevalence rates are 40–50 % in 20-year-olds. Between the two most recent iterations of National Health and Nutritional Examination Surveys (NHANES)—NHANES in 1988–1994 and NHANES in 1999–2004—the seroprevalence of HSV-2 among civilian, noninstitutionalized people aged 14–49 in the United States decreased by 19 % from 21 to 17 % [2]. By contrast, 57.7 % of the same group was seropositive for HSV-1 in 1999–2004, which represents a 6.9 % decline. Seroprevalence for HSV-2 increases with age, being virtually nonexistent in children under age 12, and stabilizing after age 30; this pattern is consistent with the virus being an STI. By contrast, HSV-1 seroprevalence in children under 5 is 20 % and rises in a linear fashion until age 20. This pattern is not characteristic of an STI. More than 85 % of the world's adult population is seropositive for HSV-1.

The NHANES surveys found that women (23.1 %) are more likely to be seropositive than men (11.2 %). Seropositivity is highest among blacks (40.3 %), followed by whites (13.7 %) and Hispanics (11.9 %). Lifetime numbers of sex partners influenced seropositivity, varying from 2.6 % of patients with no sex partners to 39.9 %, for people with at least 50 partners [2]. Patient history is very unreliable for obtaining information about this infection.

Of the 50 million Americans who are HSV seropositive, only 9 % is aware of having had a previous infection [3]. Even when seropositive individuals are asked specific questions, only 25–33 % admits having had symptoms consistent with genital herpes. Approximately 75 % of source partners discover their own infection only when their newly infected partner is diagnosed [4].

It is estimated that there are 1.6 million new cases of genital HSV infections in the United States each year [5], and 10 million recurrences annually [6]. Worldwide, 20 million new people are infected each year [7].

Herpes infections are troubling enough by themselves, but they also represent a risk factor for acquiring and spreading other STIs. Herpes is one of the most common infections found in HIV-infected adults; 90 % of HIV patients are also infected with HSV (see Chap. 4). Several studies have established a causative relationship between HSV genital ulcerations and HIV acquisition, transmission, and progression [8]. High titers of HIV are found in genital herpes ulcerations [9]. In addition, HIV infection reactivation is accompanied by an increase in plasma HIV viral load [10]. A meta-analysis of studies that documented HSV-2 infection before HIV acquisition found that the HSV more than doubled the risk; the relative risk was 2.1 (95 %, C1: 1.4–3.2). About 52 % of HIV infection is attributable to HSV-2 coinfection. The population attributable risk percentage varied with HSV-2 prevalence and ranged from 19 to 47 % [11].

Risk Factors

HSV-2 infects all economic classes, race, ages, and ethnic groups. However, there are identifiable risk factors for HSV-2 infection, which reflect biological and behavioral influences. Major risk factors for seropositivity include female gender, ethnicity (African-American or Hispanic), history of STIs, increasing number of sex partners, sexual contact with commercial sex workers, cocaine use, and low socioeconomic status or level of education. In addition, older age and young age at sexual debut are important factors [12]. Each additional sex act per week increases the risk of acquiring genital herpes [13]. In a study of discordant monogamous couples, risk factors for HSV acquisition were female gender and the absence of HSV-1 antibodies [4]. Other risk factors that have been shown to be independent predictors of HSV-2 infection in women include cigarette smoking, douching, history of having intercourse with an uncircumcised male partner, the presence of vaginal group B streptococcus, and abnormal vaginal flora [14].

Infectivity and Transmission

Herpes is highly contagious. In a study of newly acquired HSV infections the median number of sex acts before transmission was 40 [45]. Seventy-five percent of sexual partners of HSV-2-infected people contract the disease. In a study of seronegative sexually active individuals, the annual rates of infection were 1.6 % for HSV-1 and 5.1 % for HSV-2 [15]; the primary route of transmission of HSV-2 infection is genital-to-genital skin contact with an infected partner who is shedding virus symptomatically or asymptomatically. HSV-2 is responsible for about 80 % of genital herpes infections, even though there are as many initial cases with HSV-1 infection, which is usually acquired through oral–genital contact, HSV-2 is more likely to cause recurrent episodes. HSV-1 genital infections are higher in men who have sex with men (MSM) [16].

Asymptomatic shedding is responsible for most of the transmission of HSV [4, 17]. HSV DNA has been detected by polymerase chain reaction (PCR) from genital samples of HSV-2-infected women on 28 % of days [18]. In discordant couples, 69 % of transmission occurred when the infected partner was asymptomatic [4]. Transmission of HSV between discordant sexual partners occurs at a rate of about 10 % per year [19]. Asymptomatic shedding is more common with HSV-2 than with HSV-1 infection [20].

Although transmission of HSV infections generally results from intimate skin-to-skin contact with an infected individual, it can also result from exposure to infected saliva, semen, vaginal secretions, or fluid from active herpetic lesions.

Drying and room temperature quickly inactivate the virus. Therefore, HSV transmission is not believed to occur often through exposure to fomites.

Etiology

HSV belongs to the Herpesviridae family, which also includes the cytomegalovirus, Epstein–Barr virus, and varicella-zoster virus. HSV-1 and HSV-2 are two of the eight human herpes viruses; neither is found in other animal species.

HSV is an enveloped, double-stranded DNA virus. HSV-1 and HSV-2 are distinguished by antigenic differences in their envelope proteins [4]. However, the genomes of the two viruses are 50 % homologous. There are multiple specific strains of HSV-1 and HSV-2.

After contact with abraded skin or mucosal surfaces, the virus replicates and initiates infection in the epidermal cells of the target area. Following this initial infection, the virus travels in a retrograde fashion within axons of sensory nerves to the dorsal nerve root ganglion where it continues to replicate to establish lifelong latency [3]. HSV-2 usually migrates to the sacral nerve roots (S2, S3, and S4). Recurrent outbreaks localized to the dermatomes innervated by the infected nerve are quite common, especially with HSV-2. In patients with an initial primary episode of genital herpes, the risk of having at least one recurrence during the first year is nearly 90 % [21]. Although some HSV-2-infected patients may not experience symptomatic recurrences, virtually all will have repeated episodes of asymptomatic viral shedding from their genital secretions. This shedding places their sexual contacts at risk for acquiring the infection.

Clinical Manifestations

There are three types of HSV genital infections: primary infection, non-primary initial infection, and recurrent infection (see Table 2.1). A primary infection is the first HSV infection that occurs in a patient without prior exposure to HSV, as demonstrated by the fact that the patient has no antibodies to HSV. An initial,

Table 2.1 Definition of genital herpes syndromes

Initial primary infection
Initial infection with either herpes type 1 or herpes type 2 in a patient who has had no prior exposure to either HSV-1 or HSV-2 (seronegative for HSV-1 and HSV-2)
Initial non-primary infection
First clinical infection with either HSV-1 or HSV-2 in a patient who has had prior exposure to the other HSV
Recurrent infection
A recurrence, not a reinfection. The infection results from reactivation of a latent virus

Source: Modified from [26], p. 102

HSV herpes simplex virus

non-primary infection is defined as a first HSV infection with one HSV type in a patient who is already infected with another type of HSV (e.g., a new HSV-2 infection in a patient with prior HSV-1 infection). Because HSV-1 is so prevalent, most initial genital infections (usually with HSV-2) are initial, non-primary infections. Recurrent infections are outbreaks owing to reactivation of a previously acquired HSV infection (not a reinfection).

The incubation period after genital exposure to HSV-1 or HSV-2 is approximately 4 days (range 2–12 days) [22]. Almost half of first-episode genital herpes is caused by HSV-1. The local and systemic symptoms with primary genital infections are generally the same intensity and duration for both HSV-1 and HSV-2 [23].

The classical clinical presentation of genital herpes starts with widespread multiple painful macules and papules, which then mature into clusters of clear, fluid-filled vesicles and pustules. The vesicles rupture and form ulcers. Skin ulcers crust, whereas lesions on mucous membranes heal without crusting [22]. Scarring does not usually occur after re-epithelization. Secondary bacterial infections may produce ulcers that extend into the dermis or that cause cellulitis. In women, the ulcers occur at the introitus, labia, perineum, or perianal area. Patients complain of dysuria, vulvar pain, dyspareunia, and increased vaginal discharge and bleeding. Patients may volitionally retain urine because the pain with urination is so severe. On average, initial primary infections last 12 days, but viral shedding continues for 20–21 days [24]. The infection may be spread by autoinoculation to other areas of the genitalia as well as to the buttocks and thighs and to distant sites, such as the conjunctivae. Urethral involvement is common; 82 % of patients with initial infection have urethritis with positive urethral cultures. Cervical infection, which is found in 80 % of women, causes increased vaginal discharge and postcoital spotting and bleeding. Men usually develop lesions on the penile shaft or glands. The patient usually develops tender inguinal adenopathy. Perianal infections are also common in MSM. Pharyngitis may develop with oral exposure.

Initial primary infection is associated with a higher rate of systemic involvement and greater severity of local disease than is seen with initial non-primary genital herpes infection. With primary infections, 66 % of women and 40 % of men develop constitutional symptoms such as fever, malaise, nausea, headache, myalgia,

hepatitis, meningitis, and autonomic nervous system dysfunction as a result of viremia [22]. Approximately 30 % of women and 10 % of men have headache, stiff neck, and photophobia with or without fever [22]; 4 % of individuals will develop viral meningitis [25]. The meningitis is transient and requires no treatment; it resolves without any sequelae. Infection in the sacral plexus may affect sensation in the pelvis as well as detrusor function; 10–15 % of women with initial disease will develop urinary retention that requires catheterization. This nerve dysfunction may last 6–7 weeks [3]. HIV-infected individuals are at higher risk of developing the more serious clinical manifestations, including dissemination, encephalitis, and meningoencephalitis [25].

Most initial genital herpes infections are not "classical" in their presentation. The majority of initial infections are asymptomatic or atypical; patients note nonspecific symptoms of discharge, dysuria, pain, erythema, back pain, pruritus, soreness, fissure, and folliculitis and think they have a rash, allergy, yeast infection, cystitis, zipper trauma, jock itch, or bike seat irritation [26]. Clinicians often fail to diagnose HSV infection and attribute the signs and symptoms to other diagnoses, particularly when there are only small blisters or ulcers, vaginal lesions, urethritis or cervicitis without external lesions, excoriation, fissures, or nonspecific erythema [27]. About 1 in 7 men who present with sores, blisters, ulcers, crusting, or small cuts/slits had HSV and about 1 in 9 women with redness, irritation, or rash have HSV [8]. The relative mildness of the symptoms and subtlety of the physical findings may occur because most initial infections with HSV-2 occur in people who carry antibodies to HSV-1. There are generally fewer lesions with these non-primary initial infections. Systemic symptoms develop in only 16 % of people with initial non-primary infections. The duration of infection in this situation is shorter (9 days) and viral shedding lasts only 1 week [28]. Thus, genital herpes infection should be considered routinely in any patient with genital lesions. This would include patients with genital erythema, rash, skin fissuring, pain, burning, or genital itch.

Recurrent infections are more common and occur more frequently with HSV-2 than with HSV-1 infection. Within 1 year of diagnosis of initial primary HSV-2 genital infections, 90 % of people will have at least one recurrence, whereas only 55 % of HSV-1-infected people have repeat outbreaks. In one study, nearly 40 % of the HSV-2-infected subjects had six or more recurrences [21]. Median time to recurrence with HSV-2 was 49 days, whereas median time to recurrence of HSV-1 was 310 days. Most recurrences are asymptomatic. About half of patients who recognize recurrences report prodromal symptoms, such as localized tingling, pruritus, or pain 30 min to 48 h before eruption. Some patients experience more painful and prolonged prodromes including shooting pain in the buttocks, hips, or legs for up to 5 days [22]. Recurrent herpes outbreaks are usually less severe than primary outbreaks. The numbers of lesions are generally fewer. The lesions may appear the same as in primary outbreaks but heal in half the time or they may present as fissures or vulvar erythema rather than typical ulcers. About 10–15 % patients with recurrent genital herpes will have coexisting cervical disease. Systemic manifestations do not occur with recurrences in immunocompetent patients. Over time, recurrence rates decrease [29].

Frequently, women who have HSV-related ulcers become superinfected with Candida. Prompt attention to treating that infection can decrease the patient's discomfort.

Factors other than HSV type that have been associated with frequency of recurrent outbreaks include fatigue, menstruation, intercourse, and trauma. The most common cause of recurrence of HSV in HIV-infected patients is the degree of immunosuppression. Although it is commonly believed that acute episodes of stress are associated with onset of recurrent herpes, studies have concluded that only persistent stress lasting longer than 1 week and depression are psychological stressors that are associated with onset of recurrent outbreaks [3].

Testing Techniques

Until recently, viral isolation in cell culture and determination of the type of HSV with fluorescent staining has been the mainstay of herpes testing in patients presenting with characteristic genital lesions. The cytopathic cell changes induced by the herpes virus in tissue culture usually occurs within 3 days of inoculation but the cell culture is not considered negative for herpes until a final negative reading on day 15. The rate of recovery of the virus depends on the stage of the clinical disease being tested. There is a 90 % chance of obtaining a positive culture when the specimen is obtained from the base of a freshly unroofed vesicle or pustule, but that sensitivity decreases to 70 % when the specimen is obtained from an existing herpes ulcer and drops to only 27 % when a crusted lesion is used as a specimen source. The probability of recovery of the virus from a patient with recurrent herpes, which has a much shorter duration of viral shedding and a lower viral load, is only 30 %.

The Tzanck preparation is a histological examination of lesions that identifies the presence of a DNA virus with multinucleated giant cells typical of HSV. Although the test is rapid, it is not specific for HSV. Similar changes can be found in sites infected with the varicella virus. Similarly, cytological detection of HSV infection (e.g., from pap smear) is not only insensitive, it is nonspecific and has a low positive predictive rate. It should not be used for diagnosis.

PCR assay for HSV DNA has been shown to be more sensitive than viral culture and has a specificity that exceeds 99.9 %. The PCR test is the standard of care test for the diagnosis of herpes central nervous system infection. The PCR is highly accurate and faster than tissue culture. Its use in clinical practice is currently expanding due to its higher sensitivity than traditional tissue cell culture [30].

Commercially available blood tests that can identify prior exposure by testing for HSV-specific glycoproteins G2 (HSV-2) and G1 (HSV-1) immunoglobulin (IgG) G antibodies. These two Food and Drug Administration (FDA)-approved tests for laboratory use are HerpeSelect™-1 enzyme-linked immunosorbent assay (ELISA) IgG, and HerpeSelect 1 and 2 Immunoblot IgG (for HSV-1 and HSV-2) (Focus Diagnostics, Herndon, VA). They have a sensitivity of detecting HSV-2 of 98 % and

Table 2.2 Guidelines for type-specific HSV serological tests

Diagnosis of genital lesions/symptoms: type-specific serology tests should be available for diagnostic purposes in conjunction with virological tests at clinical settings that provide care for patients with STDs or those at risk at risk for STDs. Serology tests may be useful in the following situations
A culture-negative recurrent lesion
A history suggestive of herpes/atypical herpes with no lesions to culture
The first presentation of genital symptoms when culture or antigen detection is negative or not available
Screening for HIV-positive patients should be generally offered
Patients in partnerships or considering partnerships with HSV-2 infected people (especially if it would change behavior)
HIV-infected people may benefit from testing during their first evaluation
Universal screening in pregnancy should not be generally offered
Screening in general population should not be generally offered
Herpes education and prevention counseling is necessary for all people being screened for HSV-2

HSV herpes simplex virus, *STD* sexually transmitted disease, *HIV* human immunodeficiency virus

a specificity of 97–100 % because of their ability to detect glycoprotein G-2 for HSV-2 and glycoproteins G-1 and C-1 for HSV-1. Two point-of-care tests are also available: Biokit HSV-2 and SureVac HSV-2.

The older tests should never be ordered to determine a specific type of herpes. Seroconversion of an initial primary herpes attack will usually occur 12 weeks after the outbreak [30]. Therefore, HSV-2 serological testing cannot detect a primary infection; it can be used only to rule out recurrent infections. The CDC list of appropriate use of serologic testing is summarized in Table 2.2.

Screening in the general population should generally not be offered. More detail of situations in which testing might be appropriate is provided here.

1. Diagnosis of HSV-2
   (a) Patients who present with a 3-month or greater history of recurrent genital lesions suggestive of recurrent genital herpes but have no lesions on exam or have recent negative viral culture for herpes. A negative HSV-1 and HSV-2 serological test would rule out genital herpes as the cause of the lesions, whereas a positive HSV-2 serology would support the diagnosis of recurrent genital herpes. Interpretation of a positive HSV-1 test would be more difficult. However, it must be recognized that the recurrent symptoms may be owing to an unrelated lesion.
   (b) Patients who have first presentation of genital symptoms when culture or antigen detection is negative or not available. Note: testing would have to be delayed by 12 weeks to allow for antibody formulation.
2. HIV-infected patients. Because of the high coinfection rate with HSV, all HIV-infected patients should be offered type-specific HSV serological testing.
3. Partner consideration. The evaluation of patient who is in a partnership or is considering partnership with a person with documented genital herpes and is

concerned about the possible transmission. If the asymptomatic person is HSV-2-seropositive, then the couple can be reassured that further transmission between them cannot take place. If the asymptomatic person is seronegative, then the couple should be counseled regarding preventive measures (condom use) to reduce the chance of transmission.

4. Screening can be selectively offered to those patients as part of a comprehensive evaluation of individuals with a STI and those who are at risk for STIs.
5. Pregnancy applications. The CDC recommends against universal screening in pregnancy. However, screening should be offered to asymptomatic pregnant women whose partners have genital herpes, as well as prenatal patients who are HIV-infected. Discordant couples with an infected man should be counseled regarding the risk of acquiring and transmitting herpes and advised about preventive measures (e.g., abstinence during the third trimester) to avoid an initial primary infection. If the woman is seropositive, she should be counseled regarding the signs and symptoms of genital herpes near term and counseling on plans for route of delivery (see "Pregnancy-Related Issues").
6. Other authors have suggested a broader utilization of serological testing in clinically apparent initial infections, although these applications have not been endorsed or found to be cost effective. These authors have suggested that an HSV-2 titer could be used to counsel women on the likelihood of recurrence (HSV-2 is more likely to occur than HSV-1 infection). Others have recommended routine serological testing for both HSV-1 and HSV-2 antibodies to establish if the clinical outbreak is a primary, non-primary, or a recurrent lesion. The rationale is that if the patient has an HSV infection and if the serology is HSV-1- and HSV-2-negative, then the patient has an initial primary outbreak with exposure during the 14 days before the onset of symptoms. On the other hand, if the serology is HSV-1-positive but HSV-2-negative, then this is an initial non-primary outbreak; in such settings, one could probably come to that conclusion because 80 % of genital herpes is HSV-2. However, the patient would require a repeat testing for HSV-2 in 3 months to confirm this diagnostic impression. If the serology is HSV-2-positive, then the patient has an initial non-primary clinical outbreak of recurrent genital herpes with exposure sometime more 14 days prior.

Diagnosis

The clinical diagnosis of genital herpes can be difficult. This is because the infection presents with "nonclassical" or atypical characteristics or with no symptoms at all. Although the most common cause of genital ulceration is an HSV infection, other etiologies should be considered, including chancroid, traumatic ulceration, primary syphilis, Behçet's syndrome, recurrent aphthous ulcers, fixed drug reaction, Crohn's disease, contact dermatitis, Reiter's syndrome, psoriasis, erythema multiforme, and lichen planus [22]. The clinical diagnosis of genital herpes should always have laboratory confirmation, if possible.

For the last 20 years, the gold standard for diagnosis has been a positive viral culture. However PCR testing is more sensitive than viral culture (see "Testing Techniques"). Viral culture results can be available in 48–72 h and have a false-negative rate of 5–30 %. Patients who present with new onset of genital herpes should also be tested for HIV infection. Testing for other STDs depends on the clinical presentation. Cultures are more likely to detect the virus if they are obtained from the freshly exposed base of a newly ruptured vesicle than if they come from an ulcerated or crusted lesion. Primary infections are more likely to produce positive result than are recurrent infections. Because of the transient nature of viral shedding, a negative culture does not exclude genital herpes. In the patient who has recurrent infections in which isolation of the virus has been difficult, one option is to have the patient return for viral cultures 1 or 2 days into the next outbreak. Another option is to order serological testing for type-specific HSV antibodies to rule out recurrent infections as described earlier.

Treatment

The CDC recommended therapies for initial infections and episodic and suppressive therapies for recurrent infection are displayed in Table 2.3.

Treatment Recommendation for Initial Herpes Genitalis

All patients with initial clinical episodes of symptomatic genital herpes should be treated with an antiviral agent for 7–10 days or until the lesions clear. Local measures, such as saline irrigation, sitz baths, topical anesthesia, use of electric blow dryer on cool setting, and warm compresses are helpful to prevent secondary infection of the lesions and to offer comfort. Careful attention must be paid to limit the spread of infection by autoinoculation. Because the effectiveness of antiviral therapy is dependent on initiation of therapy as early in the clinical stage of disease as possible, treatment with antivirals should be started based on presumptive clinical diagnosis alone, before culture results are available.

The CDC lists three different drugs in four different treatment options for initial clinical episodes of genital herpes (see Table 2.3) [31]. Acyclovir (Zovirax™) was the first drug approved for the treatment of genital herpes. Acyclovir is a purine nucleoside analog that is a competitive inhibitor of viral DNA polymerase. Acyclovir completely inactivates the viral DNA polymerase and terminates viral DNA chain elongation. If given early in the initial stage of HSV infection, acyclovir will reduce the duration of symptoms by an average of 2 days, the time to heal the ulcers by 4 days, and viral shedding by 7 days compared to placebo [4]. In contrast to valacyclovir and famciclovir, acyclovir has poor oral bioavailability and a relatively short

Table 2.3 Treatment of genital herpes—CDC STD treatment guidelines 2010

Agent	Regimen
First clinical episode	
Acyclovir	400 mg orally 3 times a day for 7–10 days[a]
	200 mg orally 5 times a day for 7–10 days[a]
Famciclovir	250 mg orally 3 times a day for 7–10 days[a]
Valacyclovir	1 g orally twice a day for 7–10 days
Severe disease	
Acyclovir	5–10 mg/kg body weight intravenously every 8 h for 2–7 days or until clinical resolution is attained, followed by oral antiviral therapy to complete at least 10 days of therapy
Episodic therapy for recurrent genital herpes	
Acyclovir	400 mg orally 3 times a day for 5 days
	800 mg orally twice a day for 5 days
	800 mg orally three a day for 2 days
Famciclovir	125 mg orally twice a day for 5 days
	1000 mg orally twice daily for 1 day
	500 mg once, followed by 250 mg twice daily for 2 days
Valacyclovir	500 mg orally twice a day for 3 days
	1 g orally once a day for 5 days
Daily suppressive therapy for recurrent genital herpes	
Acyclovir	400 mg orally twice a day
Famciclovir	250 mg orally twice a day
Valacyclovir	500 mg orally once a day
	1 g orally once a day

From Workowski KA, Berman S. Sexually transmitted diseases treatment guidelines, 2010. Centers for Disease Control and Prevention. Division of STD Prevention National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention. MMWR Recomm Rep 2010;59 (RR-12):1–110

[a]Treatment may be extended, if healing is incomplete after 10 days of therapy

intracellular half-life, which means that acyclovir requires a three-times-a-day oral dosing schedule. For severe herpes infection requiring hospitalization, an intravenous formulation of acyclovir is available. The advantage of oral acyclovir therapy over other oral agents is lower cost, small tablets, and the availability of a liquid formulation. The disadvantages of oral acyclovir are the three-times-a-day dosing frequency.

Valacyclovir (Valtrex™) is a prodrug of acyclovir that is converted to acyclovir in the liver. The oral bioavailability of valacyclovir is much better than acyclovir and approaches the level of intravenous acyclovir. The advantage of valacyclovir is a twice-daily dosing schedule. The disadvantage of valacyclovir is higher cost and unavailability of nonoral formulations.

Famciclovir (Famvir™) is the oral form of penciclovir, a nucleoside analog with properties similar to acyclovir with an improved oral bioavailability [32]. Famciclovir is more expensive than acyclovir.

All oral antiviral agents have been shown to be equally effective [3]. Acyclovir, valacyclovir, and famciclovir have excellent safety profiles with few adverse side effects. It is estimated that more than 80 million people have taken either acyclovir or valacyclovir without significant complications [33]. HSV infections that are resistant to any of the recommended antiviral therapies are rare and generally restricted to immunocompromised patients. If resistance to acyclovir/valacyclovir/famciclovir develops, foscarnet 40 mg/kg body weight intravenously every 8 h is frequently effective. Compounded topical cidofovir gel 1 % applied to lesions once daily for 5 days also might be effective. Acyclovir has been used daily by patients for more than 10 years without any significant adverse effects.

After initiation of therapy, a follow-up visit with the patient should be scheduled in 7–10 days. Test results are usually available by that time, which will provide the caregiver the opportunity to provide more extensive counseling. If examination reveals new lesions or a failure of lesions to reach the crusting phase, then an additional course of antiviral agents should be prescribed.

The use of topical 5 % acyclovir ointment is no longer an FDA-approved as treatment during the initial outbreak because the oral medication is more effective and the use of ointment increases the risk of autoinoculation. Other treatments that should be discouraged owing to documented lack of treatment efficacy include L-lysine, goldenseal, and garlic. Lithium has been noted to decrease frequency of recurrent herpes but has not been proven effective in the treatment of the initial infection [34]. According to the CDC complicated HSV such as aseptic meningitis, disseminated infections, hepatitis, or pneumonitis should be treated initially with acyclovir 5–10 mg/kg IV every 8 h for 2–7 days or until clinical improvement is observed, followed by oral acyclovir to complete at least 10 days of total therapy [35].

Treatment of Recurrent Genital Herpes

If started at the first prodromal symptoms or sign of a recurrence, antiviral treatment of episodic outbreaks will not only reduce the severity and duration of lesions, but may also completely abort the clinical attack, stopping the lesions from progressing beyond the papule stage. The episodic dosing schedules recommended by the CDC for acyclovir (Zovirax) vary by dose and duration of treatment. The episodic recommended dose for valacyclovir and famciclovir are also specified in the CDC recommendation.

The antiviral dosage schedule for suppressive therapy may be different for patients with more frequent (>10) outbreaks annually. All three antivirals appear to be equally effective in preventing outbreaks of genital herpes and reduce asymptomatic viral shedding by 80–90 %.

In serodiscordant couples, suppressive daily antiviral therapy should be strongly considered to reduce further transmission of the infection during the first year when the incidence of asymptomatic viral shedding is highest. However, it should be noted that many couples who are discordant for genital herpes by patient history are

found to be concordant by serological testing. Year-long suppressive therapy or longer should be offered to patients with frequent recurrent outbreaks, initial primary infections or patients with stressful or painful recurrences.

Immunocompromised patients are more likely to have prolonged or severe episodes of herpetic outbreak. Higher dose therapy is recommended for episodic therapy for HIV-infected persons, e.g., acyclovir 400 mg orally 3 times daily for 5–10 days; famciclovir 500 mg orally twice daily for 5–10 days; or valacyclovir 1.0 g orally twice a day for 5–10 days. For daily suppressive therapies, acyclovir 400–800 mg is recommended orally twice to 3 times a day or 500-mg doses of famciclovir or valacyclovir orally twice a day.

Counseling

The patient diagnosed with genital herpes may have more difficulty dealing with the psychological impact of the infection than with the physical discomfort. Studies have documented that patients frequently report anger, guilt, decreased self-esteem, loss of interest in intimacy or sex, fear of transmission to their sexual partner, and difficulty with personal relationships because of their diagnosis [36]. Mental and physical health scores in patients diagnosed with genital herpes were lower than the general population [24]. Although it is not currently possible, patients want reassurance that their genital herpes will never recur. Most patients will eventually accept their diagnosis and learn to cope with this chronic condition.

The goals of counseling are patient education, partner notification (in order to break the chain of transmission), education on recognizing outbreak episodes, availability of treatment for viral transmission, as well as risk-reduction maneuvers. The 2006 CDC Guidelines also provide guidance about patient counseling (see Table 2.4). In general, counseling of patients with recurrent herpes should emphasize that there is no known therapy to prevent establishment of latency of the herpes virus in the sensory ganglia of the sacral plexus or to prevent recurrent disease. In other words, there is no cure for herpes. The patient with recurrent disease should avoid intercourse during outbreaks beginning at the onset of prodromal symptoms until crusting over of the lesions several days later. Another option is to use latex condoms at all times, but particularly during genital outbreaks. Information about local self-help and support groups can be helpful.

The major concern of patients with genital herpes remains the fear of transmission to their sexual partners. In serodiscordant couples the transmission is most likely to occur in the first 3–6 months. It is estimated to occur at a rate less than 10 % per year thereafter owing to decreased incidence of viral shedding and clinical outbreaks [19].

Patients should also be advised about the risks of neonatal herpes and the strategies that should be taken to prevent vertical transmission.

Table 2.4 2006 CDC counseling guidelines for patients with herpes genitalis

Information about the natural history of the disease, with emphasis on the potential for recurrent episodes, asymptomatic viral shedding, and attendant risks of sexual transmission
Information about episodic or suppressive treatment with antiviral medication to shorten the duration of or prevent symptoms
All patients with genital HSV infection should be encouraged to inform their current sex partners that they have genital herpes and to inform future partners before initiating a sexual relationship
Persons with genital herpes should be informed that sexual transmission of HSV can occur during asymptomatic periods. Asymptomatic viral shedding is more frequent in genital HSV-2 infection than in genital HSV-1 infection and is most common in the first 12 months following acquisition of HSV-2, but may persist for years, less frequently, in some individuals
Patients should be advised to abstain from sexual activity when lesions or prodromal are present
The risk of HSV sexual transmission can be decreased by the daily use of antiviral agents by the infected person
Latex condoms, when used consistently and correctly, can reduce the risk of genital herpes when the infected areas are covered or protected by the condom
Sex partners of infected persons should be advised that they might themselves be infected even if they have no symptoms. Type-specific serological testing of asymptomatic partners of persons with genital herpes can determine whether risk for HSV acquisition exists
The risk of neonatal infection should be explained to all patients, including men. Pregnant women and women of childbearing age who have genital herpes should inform their providers who care for them during pregnancy, as well as those who will care for their newborns infants. Pregnant women who are not infected with HSV-2 should be advised to avoid intercourse during the third trimester with men who have genital herpes. Similarly, pregnant women who are not infected with HSV-1 should be counseled to avoid genital exposure to HSV-1 (e.g., oral sex with a partner with oral herpes and vaginal intercourse with a partner with genital HSV-1 infection) during the third trimester
Asymptomatic persons diagnosed with HSV-2 infection by type-specific serological testing should receive the same counseling messages as persons with symptomatic infection. In addition, such persons should be taught about the clinical manifestations of genital herpes

HSV herpes simplex virus, *HIV* human immunodeficiency virus

Pregnancy-Related Issues

About 22 % of pregnant women are infected with HSV-2 and 2 % will acquire HSV during pregnancy [37]. Initial HSV infection is particularly severe if it develops during pregnancy; pregnancy does not appear to increase the rate of recurrence of maternal outbreaks.

The most serious consequences of maternal infection are adverse fetal impacts and newborn infection. An initial maternal genital herpes outbreak in the first trimester of pregnancy has been associated with fetal chorioretinitis, microcephaly, and skin lesions but not spontaneous abortion or fetal death [38]. Neonatal HSV infection occurs in about 1,500 cases each year [39, 40]. Neonatal HSV infection has three clinical presentations: disseminated disease involving multiple organs, such as the liver, lungs, and the central nervous system (25 % of cases); disease localized to the skin, eyes, and mouth (40 % of cases); and localized central nervous system disease (35 % of cases). Up to 30 % of infected neonates will die and up to 40 % of survivors will have neurological damage, despite antiviral therapy [40].

Infection can be transmitted from the mother to her fetus/newborn in three ways: transplacentally (5–8 %), intrapartum exposure (85 %), or postpartum exposure (8–10 %) [39]. The likelihood and severity of neonatal infection is influenced by the mother's antibody status. If a woman develops initial primary infection during pregnancy, there is a 5 % chance of transplacental transmission to the baby.

Most neonatal infections result from fetal exposure during delivery. The remaining confirmed cases of neonatal herpes may have been acquired postnatally, either from the mother, a relative, or hospital worker as a result of oral contact or contact with an infected finger (whitlow) [41].

Neonatal herpes infections develop in 30–50 % of exposed infants whose mothers have an initial primary infection near time of delivery [10]. The risk of neonatal herpes from an asymptomatic mother with a history of recurrent HSV at term or who acquire HSV in the first-half of pregnancy is much lower (<1 %). Only infants delivered to women who are actively shedding from recurrent infections at the time of delivery will acquire infection. It has been estimated by PCR techniques that 6–10 % of HSV-2-seropositive women shed virus in labor [42]. However, because of the ubiquitous nature of this infection, more neonatal infections result from recurrent infections than from initial maternal infections. Infrequently, the infant may be infected by a caregiver with oral herpetic lesion or herpes whitlow, which involves the distal fingers.

The role of testing for HSV infection in pregnancy is under debate. The cost-effectiveness of routine HSV screening in pregnancy is controversial [43, 44].

It has been suggested that type-specific HSV-2 serology testing be performed on women who have no personal history of HSV but whose partners are known to be infected. Women who tested negative could be advised to avoid sexual contact, at least during the third trimester and encouraged to use condoms (or abstinence) throughout the rest of pregnancy. The effectiveness of antiviral therapy for the partner to decrease the risk of HSV transmission to pregnant women has not been studied.

Women who develop primary HSV infection during pregnancy should be treated with acyclovir [40, 45]. Acyclovir, valacyclovir, and famciclovir are classified as pregnancy category B drugs by the FDA. More than 1200 pregnancy outcomes have been followed in infants exposed in utero at all stages of fetal development to acyclovir. No significant differences in rates of birth defects or adverse pregnancy outcomes have been reported [33]. Experience with valacyclovir and famciclovir is too limited in the CDC estimation to provide information about the safety of its use in pregnancy.

For women who are known to have recurrent outbreaks of genital lesions, suppressive therapy with antiviral agents starting at 36 weeks gestational age has also been shown to reduce the rate of symptomatic outbreaks and asymptomatic shedding and the need for cesarean section [46]. Therefore the American College of Obstetricians and Gynecologists advise beginning acyclovir 400 mg three-time-a-day or valacylovir 500 mg twice a day from 36 weeks until delivery [47]. The use of scalp monitors in labor should be discouraged in women who are known to shed HSV, but the American College of Obstetricians and Gynecologists says the use is not contraindicated if needed to assess fetal condition adequately in women with a history of HSV but without symptoms or lesions.

Cesarean delivery is recommended for women who have active genital lesions or prodromal symptoms at the time of rupture of membranes or labor. Operative delivery has been shown to reduce the risk of transmission significantly in initial infection. Vaginal delivery is recommended for women who do not have lesions or symptoms at the time of delivery. C-section is not needed if the patient has lesions in extra-genital areas, such as the buttocks or legs. The lesions can be covered and the patients can be allowed to deliver vaginally.

The pediatrician should always be informed of the maternal/patient history of herpes and the status of the mother at the time of delivery. Acyclovir may be recommended if the mother acquired the infection during pregnancy (especially third trimester) pending the results of the maternal and/or newborn culture.

Breastfeeding is not contraindicated except in mothers who have active HSV infections on the nipple or other sites on their breasts. Mothers should use caution when handling newborns and may take antiviral therapies when breastfeeding to diminish shedding.

Partner Notification and Reporting Requirements

HSV is not a reportable disease in most states. Patients should be advised to talk with their sex partners about their diagnosis. If the partner is infected with the same HSV type, no precautions need to be taken. Patients should understand most infected partners are not aware that they carry the virus. All new sex partners should be informed of the potential for infection and that safer sex practices may reduce, but do not eliminate, the possibility of transmission.

Prevention

Latex condoms are impermeable to passage of the 160 nm HSV-2. In 2002, a National Institutes of Health expert panel reviewed the literature and found that there was not sufficient data to allow it to form any conclusions about the effectiveness/ineffectiveness of correct and consistent condom usage in reducing the risk of genital herpes infection [6]. However, a subsequent study of discordant couples found that when condoms were used more than 25 % of the time, the risk of transmission to an uninfected woman was reduced by more than 90 % (see Chap. 14) [12]. More recently, analysis of data collected as part of a clinical trial of an ineffective candidate vaccine for HSV-2 revealed that those who reported more frequent condom use were at lower risk for acquiring HSV-2 than those who used condoms less frequently [48]. Counseling for consistent condom use is needed because, despite the fact that there is a risk of transmission from asymptomatic shedding, couples are less likely to use condoms when active lesions are absent [49].

Chronic suppressive therapy is effective in preventing both clinical recurrences and asymptomatic viral shedding. Avoiding sexual contact during episodes of known clinical outbreaks will prevent transmission of HSV. Several vaccines are currently being tested in Phase III clinical trials but the development of an effective vaccine to prevent genital HSV has been challenging (see Chap. 15) [50].

Selected Resources

American Social Health Association

A comprehensive resource for patients, their partners, and care givers. Offers herpes prevention, screening, and disease management information.
Home of the National Herpes Resource Center
Web site: http://www.ashastd.org/std-sti/Herpes.html
Phone: 800-783-9877 for a free catalog

The International Herpes Management Forum

Wide range of herpes issues for both physicians and patients.
Web site: http://www.ihmf.org/Patient/PatientResources.asp

Fact Sheet on Genital Herpes

From the CDC National Center for HIV, STD, and TB Prevention in the Division of Sexually Transmitted Diseases.
Web site: http://www.cdc.gov/std/Herpes/STDFact-Herpes.htm

National STD Hotline

Health information hotline dedicated to providing accurate, basic information, referrals, and educational materials on a wide variety of STDs. Hotline specialists answer basic questions about STDs and refer callers to public health clinics and other local resources.
Phone: 800-232-4636 (24 h in English and Spanish).

National Herpes Hotline

Operated by American Social Health Association (ASHA) as part of the National Herpes Resource Center.
Free counseling on herpes as well as referrals.
A list of local support groups is available at: http://www.ashastd.org/hrc/help grp1.html
Phone: 919-361-8488
(9 AM–6 PM Eastern Standard Time, Monday through Friday) Web site: http://www.herpesonline.org

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