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Update on antiviral therapy for genital herpes infection

■ ABSTRACT

For the primary infection of genital herpes, antiviral therapy with acyclovir is the gold standard. For recurrences, there are two options: antiviral treatment of each outbreak as it arises, or suppression of outbreaks with daily oral therapy. Patients tend to prefer the latter because it can decrease the number and severity of outbreaks, but it increases asymptomatic viral shedding and, therefore, the risk of unwittingly transmitting herpes simplex virus to uninfected sexual partners.

■ KEY POINTS

Suppressive antiviral therapy is recommended for patients with frequent outbreaks (eg, six or more per year) or severe symptoms.

Studies showed that infected women asymptotically shed virus from the genital tract on 2% to 6% of days on which cultures were performed, and that women with a higher rate of symptomatic recurrences had a higher rate of asymptomatic HSV shedding.

Suppressive therapy increases the likelihood of asymptomatic viral shedding. Counsel patients about the use of barrier methods with uninfected sexual partners.

Many of the antiviral agents are renally excreted and require adjustment for patients with renal failure.

*The authors discuss off-label uses of medications.

GENITAL HERPES PRESENTS a dual challenge to the clinician: how to treat the potentially virulent first episode, and how to treat recurrences in a way that is acceptable to the patient, yet minimizes the risk of asymptomatic shedding of virus to uninfected sexual partners.

Acyclovir was the first antiviral agent available to treat primary infections and recurrences, and a number of newer agents are now available.

■ PREVALENCE

Herpes simplex infection is the most common cause of genital ulcer disease, with more than 30 million people infected in the United States.¹ Both herpes simplex virus (HSV) type 1 and type 2 cause genital herpes, but HSV type 2 is responsible for 70% to 90% of cases. The seroprevalence of HSV-2 is especially high among women of reproductive age.^{2,3} Symptomatic recurrences are common.

■ PATHOGENESIS

HSV is a double-stranded DNA virus of the family Herpesviridae. Direct contact with secretions or with mucosal surfaces contaminated with the virus can lead to HSV infection. The virus can enter the skin through cracks but readily penetrates intact mucosal surfaces; it replicates locally in parabasal and epithelial cells, causing cell lysis and inflammation. The incubation period is 2 to 7 days after initial contact. HSV eventually follows the peripheral sensory nerves to the dorsal root ganglion, where latent infection is estab-

lished. Once infected with HSV, a person has the potential for recurrent infections.

■ CLINICAL PRESENTATION OF GENITAL HERPES

Primary infection in patients with no previous exposure

In patients not previously exposed to HSV-1 or HSV-2 (ie, who lack antibody to HSV-1 or HSV-2), the primary infection may be subclinical, but more often it is severe.

Patients usually experience a prodrome of fever, myalgia, malaise, and tender bilateral inguinal adenopathy, followed by multiple painful vesicles that may ulcerate. In women, lesions are usually found on the perineum, vulva, labia, vagina, or cervix, and in men on the shaft of the penis, prepuce, or glans. In some women, urethral involvement may result in severe dysuria, occasionally requiring catheterization. Herpetic sacral radiculomyelitis may develop in women and in men, leading to neuralgia, obstipation, and urinary retention. Other symptoms may include herpetic sacral radiculomyelitis, headache, and aseptic meningitis.⁴ Primary infection can persist for several weeks before healing occurs.

Primary infection in patients with previous exposure

Some patients who present with a primary genital herpes infection have been previously exposed to HSV through oral infection—ie, they have antibodies to HSV-1 or HSV-2 on presentation. In these patients, the infection is milder, with fewer systemic symptoms, fewer vesicles, less pain, and a shorter period of viral shedding.

Recurrences of genital herpes infection

Most patients with symptomatic primary infection have symptomatic recurrences.^{5,6} In one review,⁵ 89% of patients with HSV-2 infection had at least one recurrence during a median follow-up of 418 days. The median number of recurrences was four per year, but 38% of patients had six or more, and 20% had more than 10. Recurrences were more frequent in patients with more severe primary infection, younger age at acquisition, and longer duration of primary infection. Patients with genital her-

pes caused by HSV-1 have far fewer recurrences than those with HSV-2 infection.

The rate of recurrence appears to decrease over time in most patients followed for at least 5 years; however, only one third of patients in a recent study⁷ experienced a clinically meaningful decrease in recurrences during the first 2 years, and recurrence rates were not affected by the use of antiviral therapy for the first episode of infection.

Recurrent infections are generally less severe than the primary infection; nevertheless, they can be physically and psychologically damaging.

Factors that initiate recurrences include menstruation, stress, sun exposure, and sexual intercourse. Recurrences are often accompanied by a prodrome of dysesthesia, pruritus, or tingling 48 hours preceding the eruption of the vesicles.

Asymptomatic viral shedding

When recurrences are asymptomatic, the risk of viral shedding^{2,8-10} to uninfected sexual partners is high.

Studies of the frequency of and risk factors for asymptomatic viral shedding^{6,9} showed that infected women asymptotically shed virus from the genital tract on 2% to 6% of days on which cultures were performed,^{8,9} and that women with a higher rate of symptomatic recurrences had a higher rate of asymptomatic HSV shedding, as detected by culture methods.⁹ The rate of asymptomatic viral shedding is likely higher than 2% to 6%, because HSV-DNA as detected by polymerase chain reaction (a more sensitive test) was 3.5 times higher than the isolation rate from standard culture of the same samples.¹¹

In men, subclinical viral shedding occurs less often (on 2% of days cultured).

In both men and women, higher rates of viral shedding occur among patients with concurrent human immunodeficiency virus (HIV) infection.

■ DIAGNOSIS

The classic clinical appearance of grouped vesicles in addition to features in the history and physical examination establish the diagnosis of genital herpes infection. Pathologically,

Patients with HSV-1 have far fewer recurrences than those with HSV-2

TABLE 1**Guidelines for use of antivirals to treat genital herpes infection**

DRUG	TREATMENT OF PRIMARY INFECTION	EPISODIC TREATMENT OF RECURRENCES	SUPPRESSIVE THERAPY
Acyclovir	200 mg orally five times a day for 7-10 days, OR 400 mg orally three times a day for 7-10 days, OR 5 mg/kg intravenously every 8 hours for 5-7 days or until resolution, OR 5% ointment topically every 6 hours for 7 days (use only if patient cannot tolerate oral acyclovir)	200 mg orally five times a day for 5 days at the first sign of symptoms, OR 400 mg orally three times a day for 5 days at the first sign of symptoms, OR 800 mg orally twice a day for 5 days either at the first sign of symptoms or if symptoms are more severe	400 mg orally twice a day
Famciclovir	250 mg three times a day for 7-10 days	125-250 mg twice a day for 5 days	250 mg twice a day
Valacyclovir	1g twice a day for 7-10 days	500 mg twice a day for 5 days	Either 500 mg orally once a day (if < 10 recurrences per year) or 1,000 mg orally once a day
Cidofovir	Not recommended for treatment of primary infection	For treatment of recurrences in patients with acyclovir-resistant strains; consult an expert	Limited data; consult an expert
Foscarnet	Not recommended for treatment of primary infection	For treatment of recurrences in patients with acyclovir-resistant strains: 40 mg/kg one to three times a day for 3-4 weeks	Limited data; consult an expert

the presence of multinucleated giant cells with characteristic intranuclear lesions (Cowdry type A) in Tzanck test scrapings from vesicular genital lesions is virtually pathognomonic.

In patients with a single ulcer and inguinal adenopathy, the differential diagnosis is more extensive and includes chancroid, lymphogranuloma venereum, granuloma inguinale, primary syphilis, and Behçet disease.¹²

Pitfalls of laboratory testing

Viral culture confirms the diagnosis, but false-negative results occur at the rate of 20% to 30%.¹³ Factors affecting the yield include inadequate sampling, method of transport, or improper handling by the laboratory. Delays in diagnosis can also occur unless rapid culturing techniques (eg, shell vial cell culture) are used. Direct fluorescent antibody staining of vesicular tissue is a rapid and sensitive (approximately 80%) way to diagnose HSV.

The sensitivity of direct fluorescent antibody staining and culture improves if specimens are collected within the first 2 to 3 days of vesicle onset.

Other diagnostic tests such as antigen capture assay, immunofluorescence, enzyme-linked immunoassay, and polymerase chain reaction are rapid and sensitive for detection of HSV. HSV immunoglobulin G antibody testing has limited diagnostic efficacy.

■ HOW ANTIVIRALS WORK

A number of antiviral drugs are available for treatment of HSV infection (TABLE 1).

Acyclovir

Acyclovir (Zovirax) is used in the treatment of acute HSV infection and in suppressive therapy. It inhibits viral replication by interfering with DNA synthesis. It is a prodrug and must be phosphorylated three times to

Adjust antiviral doses for patients with renal failure

become active. Viral thymidine kinases phosphorylate acyclovir to a monophosphate, then cellular enzymes phosphorylate it to acyclovir triphosphate, which binds to viral DNA polymerase and is incorporated into viral DNA, preventing chain elongation. Mutations in the viral thymidine kinase or DNA polymerase may result in acyclovir resistance.

Acyclovir is widely distributed in tissues and is renally excreted, so the dosage must be reduced in patients with renal failure. Oral, parenteral, and topical forms are available, but topical acyclovir is substantially less effective than oral and parenteral forms, and its use should be discouraged. **TABLE 1** lists the various dosage schedules.

Adverse effects. Major adverse effects of acyclovir include nausea, vomiting, renal dysfunction, and (rarely) headache and hematologic abnormalities.

Famciclovir

Famciclovir (Famvir) is used in the treatment of acute outbreaks of genital herpes infection and in suppressive therapy for HSV. It is an oral prodrug of penciclovir. After absorption, famciclovir is converted to penciclovir through deacetylation and oxidation.¹⁴ Penciclovir requires the same triphosphorylation steps as acyclovir. Viral resistance to penciclovir may result from mutations in the viral gene coding for thymidine kinase.

Famciclovir is available only in tablet form. It is renally excreted, and dosage must be adjusted in patients with renal failure.

Adverse effects include headache, dizziness, nausea, and diarrhea.

Valacyclovir

Valacyclovir (Valtrex) is used in the treatment of acute outbreaks of HSV infection and in suppressive therapy.¹⁴ It is a prodrug of acyclovir and is converted to acyclovir and L-valine by valacyclovir hydrolase via first-pass intestinal and hepatic metabolism. Valacyclovir requires the same phosphorylation steps as the parent drug, acyclovir. Valacyclovir has enhanced bioavailability with high plasma levels of acyclovir.

Like famciclovir, valacyclovir is available only in tablet form. Since the drug is renally excreted, dosage must be adjusted for renal failure.

Adverse effects include nausea, vomiting, and diarrhea. Thrombotic thrombocytopenic purpura or the hemolytic uremic syndrome has been reported in immunocompromised patients receiving high doses of valacyclovir.¹⁴

Foscarnet

Foscarnet (Foscavir) is usually reserved for treatment of acyclovir-resistant genital herpes in immunosuppressed patients. Foscarnet should only be given in this situation after consultation with an expert, given the toxicity of the drug and the limited information on its use in genital herpes. Foscarnet works by inhibiting viral DNA synthesis by direct action on viral DNA polymerase. Unlike other antivirals, foscarnet does not require phosphorylation for activation.

Foscarnet is given intravenously in doses that must be adjusted according to the creatinine clearance.

Adverse effects include renal failure secondary to acute tubular necrosis, hypocalcemia, hypokalemia, hypomagnesemia, elevated liver function tests, hypophosphatemia, and hyperphosphatemia. Fever, headache, seizures, diarrhea, and thrombophlebitis also may occur.

Cidofovir

Cidofovir (Vistide) is a member of a new class of agents effective against a broad spectrum of herpesviruses. Although primarily used for cytomegalovirus infections, cidofovir is effective against all herpesviruses, including acyclovir-resistant isolates.¹⁴ It may be helpful in immunocompromised patients with acyclovir-resistant genital herpes in whom other less-toxic agents have not been effective. The use of cidofovir in this situation should be considered only after consultation with an expert.

After uptake into the cells, cidofovir is converted to cidofovir diphosphate by cellular enzymes.¹⁵ The diphosphate entity is a structural analogue of deoxycytidine triphosphate, which selectively inhibits viral DNA polymerases.

Cidofovir is given intravenously and cannot be used in any patient with serum creatinine greater than 1.5 mg/dL.

Adverse effects are nephrotoxicity and

neutropenia. Close monitoring of renal function and complete blood counts during therapy is critical.¹⁵

■ TREATMENT GOALS IN GENITAL HERPES INFECTION

For primary genital herpes infection, the goals of therapy are to relieve symptoms and to decrease viral shedding. For recurrent infections, the goals of therapy are either to relieve symptoms on each recurrence or to suppress recurrences with daily therapy.

Treating primary genital herpes infection

Acyclovir, valacyclovir, and famciclovir are effective as first-line therapy for the first clinical episode of genital herpes infection. Most clinical data on these drugs pertains to acyclovir, which has been shown to decrease the duration of acute infection and the time for lesion healing when compared with placebo. In clinical studies, valacyclovir was equivalent to acyclovir for primary genital herpes. Famciclovir has not been formally studied or approved for primary genital herpes but has been recommended as first-line therapy by a number of groups, including the Centers for Disease Control, given the likelihood that it would be equally effective. Drug resistance is exceedingly rare for all of these agents in patients with normal immune function. Outpatient therapy (eg, acyclovir 400 mg by mouth five times a day, **TABLE 1**) is usually adequate. Because topical acyclovir is significantly less effective than the oral form, it is reserved for patients who cannot tolerate oral or parenteral therapy, and its use is discouraged.

In patients with severe primary infection or systemic symptoms requiring hospitalization, parenteral therapy (5 mg/kg every 8 hours until resolution of symptoms) is often necessary. Acyclovir therapy may shorten the duration and severity of symptoms (though the effect is modest) but does not alter the frequency of recurrences.¹³

Episodic therapy for recurrent infections

Most patients who have had a primary HSV infection will have recurrences, but recurrent

infections do not always require treatment. For patients with severe recurrences, initiation of therapy at the first onset of symptoms reduces the duration of symptoms and viral shedding. Episodic treatment must be initiated within 48 hours of the first sign of symptoms to be of benefit.¹⁰ Nevertheless, episodic treatment is at best only modestly effective.

Episodic therapy is best accomplished if the patient keeps a supply of antiviral agent and begins treatment immediately when symptoms occur. The choice of antiviral agent should be individualized, since no one drug is clearly more effective. Important considerations include the total pill burden per day, the number of daily doses, the cost, and the availability of the drug in generic form. Acyclovir, valacyclovir, and famciclovir are all generally well tolerated, although some patients may experience minor adverse effects with one drug and not the others.

Suppressive therapy

Patients usually prefer suppressive therapy. Currently, suppressive therapy with acyclovir, valacyclovir, or famciclovir is recommended for patients with six or more episodes per year, or for those whose outbreaks are severe (**TABLE 1**).^{9,10,13,16,17} Again, the selection of the most appropriate antiviral agent for chronic suppressive therapy should be individualized.

Given the daily use of these drugs over a typical 2-year period or longer, the cost of the drugs becomes an even more relevant issue. Daily suppressive therapy with acyclovir has proven safe for treatment courses lasting longer than 6 years; limited information is available about the safety of valacyclovir and famciclovir for treatment courses longer than 1 year.

Advantages. Outbreaks can occur while on suppressive therapy, but they are usually less severe. Suppressive therapy can decrease the recurrence rate by 80% to 90%. All agents appear to have similar efficacy.

Disadvantages. Asymptomatic viral shedding can still occur while on suppressive therapy, so patients may unwittingly spread the infection to sexual partners. Also, suppressive therapy is expensive, and patients usually require treatment for 12 to 24 months. Unfortunately, recurrences are common after withdrawal of

Suppressive therapy is recommended for those with six or more episodes per year

suppressive therapy, although they may be less frequent. After 1 year of continuous therapy it may be useful to discontinue therapy and reassess the rate of recurrences. Suppressive therapy can be reinstituted at any time.

■ PATIENT COUNSELING IS ESSENTIAL

The patient and the physician must decide together which is the best treatment. But an essential part of treatment is educating patients about asymptomatic viral shedding and the likelihood of transmitting HSV despite suppressive therapy. Physicians should instruct patients about the use of condoms with each act of intercourse, stressing that condoms are not 100% protective and that patients must be responsible and inform their potential sexual partners of their infection.

■ SPECIAL CONSIDERATIONS

Perinatal genital herpes infection

The risk of an infected mother transmitting HSV to her newborn infant is high (30% to 50%) if she acquires genital herpes near the time of delivery. If the history of primary infection is more remote (ie, before pregnancy), the risk is 3%.¹

Perinatal suppressive therapy. Two small studies of suppressive therapy with acyclovir at term in pregnant women suggest it effectively prevents reactivation. However, until proof of safety and efficacy of the drug is established, suppressive therapy with acyclovir should not be used routinely in late pregnancy.

When to perform cesarean delivery. Viral cultures during pregnancy cannot predict viral shedding at the time of delivery and should not be done routinely. However, at the onset of labor, thorough examination and rigorous questioning about recent or past history of HSV disease are warranted. Women without signs or symptoms of genital HSV infection should be allowed to deliver vaginally.¹ Women with signs or symptoms of genital HSV infection should undergo cesarean delivery.

Antiviral treatment of infants born to women who acquired infection near term is recommended. All infants with evidence of

neonatal HSV infection should receive acyclovir parenterally, 30 to 60 mg/kg per day for 10 to 21 days.¹

Immunosuppressed patients

In patients with compromised immune systems, such as those with AIDS, primary genital herpes can produce large ulcers. Chronic hyperkeratotic verrucous plaques, rectal plaques and erosions, and sacral radiculopathies may occur.⁴ Lumbosacral radiculomyelopathy associated with urinary retention, paresthesia of the second and third sacral dermatomes, neuralgia, constipation, and impotence have been described.

Recurrent infections cause more necrosis in immunocompromised patients and tend to heal more slowly. Herpetic hepatitis, viremia, and encephalitis can complicate recurrent infections in these patients. In patients with HIV and recurrent HSV infections, suppressive antiviral therapy is often necessary indefinitely, and this may lead to drug resistance.

It should be noted that valacyclovir has been associated with thrombotic thrombocytopenic purpura and hemolytic uremia syndrome in several AIDS patients, an allogeneic bone marrow transplant recipient, and a renal transplant recipient. These cases were reported from early clinical trials of valacyclovir using high doses (8 g/day). This has not been reported using lower doses (500–1,000 mg/day) or with acyclovir or famciclovir.

■ DEVELOPMENT OF A HERPES VACCINE

The ideal prophylactic vaccine for HSV would protect the individual from infection caused by HSV-1 and HSV-2. Several different approaches have been used, including inactivated whole-virion preparations, plasmids expressing one or more HSV genes, replication-impaired HSV mutants, and nonpathogenic vectors that express one or more HSV antigens. Vaccine containing replicating mutants would be expected to induce a more durable immune response than vaccine containing only peptides. Several large clinical trials are underway, but useful preventive vaccination is unlikely in the near future.

Instruct patients about asymptomatic viral shedding and the risks to sexual partners

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