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Review

Treatment of herpes simplex virus infections

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Abstract

Herpes simplex virus (HSV) types 1 and 2 are ubiquitous organisms that cause infections in human populations throughout the world. The clinical manifestations of HSV infections are varied, ranging from asymptomatic disease to life-threatening illness in neonates and immunocompromised hosts. This article will review the common presentations for HSV disease and the current recommendations for the treatment of these infections. A detailed summary of the antiviral drugs used to treat HSV infections is also presented.

Keywords: Herpes simplex virus; Treatment; Antiviral drugs

1. Introduction

Over the past 40 years, antiviral agents for the treatment of infections due to herpes simplex virus (HSV) have been developed. Treatments are now available for primary (the initial infection with HSV) and recurrent disease. However, many, perhaps most, infections are asymptomatic or unrecognized, and thus individuals do not seek treatment (Ashley and Wald, 1999; Koutsky et al., 1990). Important factors to consider in selecting treatment are the immune status of the host, the site of infection, and whether the infection is primary or recurrent. In this paper, the available antiviral agents will be discussed and current recommendations for treatment of specific clinical manifestations of HSV infections, including orolabial, ocular, and genital, as well as herpes encephalitis and neonatal herpes, will be given.

HSV infections have a worldwide distribution and have been described in the medical literature for centuries. HSV exists as two types: HSV-1 and HSV-2. HSV-1 is more frequently associated with oral disease, whereas HSV-2 is more frequently associated with genital disease. However, either virus can cause clinically indistinguishable disease at a number of sites and can establish persistent (latent) infection in sensory ganglia from which the virus can reactivate to cause symptomatic or asymptomatic recurrent infection. HSV infections are among the most common diseases of humans, with an estimated 60–95% of the adult population being infected by at least one of them.

2. Pathogenesis

HSV spreads from person to person by direct contact with infected secretions. The virus enters the host through mucous membranes or abraded skin and is then transported retrograde along peripheral sensory neurons to the ganglia where it enters a nonreplicating, latent state. Periodically, HSV may reactivate from its latent state and travel anterograde along the peripheral sensory nerves to the skin or mucosal sites. Recurrent mucocutaneous shedding of HSV may or may not be associated with recognized symptoms, but in either setting, virus may be transmitted.

3. Clinical manifestations

The clinical manifestations of HSV infection depend on the portal of entry, the immune status of the host, and whether the infection is primary or recurrent. HSV commonly causes gingivostomatitis, orolabial disease, ocular disease, and genital infections. Less common skin infections include *herpetic whitlow*, *eczema herpeticum*, and *herpes gladiatorum*. Skin lesions are characteristically vesiculo-ulcerative. Potentially fatal diseases include neonatal infection, encephalitis, and disseminated infections in patients with defects in cellular immunity.

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4. Diagnosis

Isolation of HSV in tissue culture is the "gold standard" for diagnosis. Two to 7 days are usually required before typical cytopathic effects are seen. A more rapid diagnostic test for mucocutaneous lesions is direct immunofluorescent staining of skin scrapings. Use of the polymerase chain reaction (PCR) to amplify HSV DNA in the cerebrospinal fluid (CSF) is faster and more sensitive than viral culture and is the diagnostic test of choice for herpes encephalitis (Whitley and Lakeman, 1995) and can also be used to rapidly confirm infections at other sites. Type-specific serologic tests are now available and may be used to diagnose unrecognized HSV-1 and HSV-2 infections or to confirm suspected cases (Ashley and Wald, 1999; Wald and Ashley-Morrow, 2002).

5. Treatment

Treatment for primary oral or genital HSV infections in healthy patients is usually given orally for 7–10 days with acyclovir, valacyclovir, or famciclovir (Centers for Disease Control and Prevention, 2002). Treatment for recurrent disease can be episodic (treatment at the first sign or symptom of an outbreak) for 1–5 days to decrease the symptoms of HSV infection or suppressive (daily) to prevent recurrences (Stanberry et al., 1999; Corey, 2002). Suppressive therapy also decreases asymptomatic shedding and probably reduces transmission (Wald et al., 1997; Corey et al., 2002). Treatment of severe disease, such as neonatal infections or encephalitis, should be with intravenous (i.v.) acyclovir.

5.1. Gingivostomatitis and orolabial HSV infections

The most common manifestation of primary HSV-1 infection, gingivostomatitis, is characterized by vesiculoulcerative lesions in and around the oral cavity. Most cases are undiagnosed, and thus are not treated (Simmons, 2002). Some young children may require hospitalization and i.v. hydration because of pain and difficulty with swallowing. In one study, oral acyclovir treatment started within the first 3 days of symptoms shortened the duration of lesions, viral shedding, fever, and the amount of time children refused to eat or drink by 2–6 days as compared to placebo (Amir et al., 1997).

Recurrent orolabial HSV lesions (*herpes labialis*) are most often noted at the outer edge of the vermilion border of the lips and may be preceded by a prodrome of tingling or burning (Whitley, 2002). Signs and symptoms associated with *herpes labialis* are mild and untreated lesions usually resolve in 1 week. For antiviral therapy to have an effect, it should be started either with the prodrome or the first sign of a lesion. Available therapies include topical acyclovir (Raborn et al., 1988), oral acyclovir (Spruance et al., 1990; Raborn et al., 1987), penciclovir (Spruance et al., 1997), docosanol (Sacks et al., 2001; Spruance, 2002), and valacyclovir (Spruance et al., 2003) (also reviewed in Spruance and Kriesel, 2002; Vander Straten et al., 2001). Of the topical therapies, only penciclovir has been clearly demonstrated to be effective in an adequately powered and controlled clinical trial. Either topical penciclovir or oral acyclovir shortens time to healing by about 1 day. A recent study of 2 g of valacyclovir b.i.d. for 1 day in adults also reported that the duration of the episode was reduced by 1 day (Spruance et al., 2003). In contrast to the modest efficacy of antiviral therapy in episodic treatment, suppressive oral acyclovir is useful in preventing clinical recurrences (Spruance and Kriesel, 2002; Vander Straten et al., 2001; Rooney et al., 1993) and may be used at times when reactivation of latent virus is more common, such as intense exposure to sunlight.

5.2. Ocular HSV infections

HSV is the most common cause of corneal blindness in the United States. Both direct viral cytopathic effects and immune-mediated responses contribute to ocular damage. HSV ocular infection is characterized by either unilateral or bilateral follicular conjunctivitis with dendritic lesions of the cornea. Prompt referral to an ophthalmologist is required for diagnosis and treatment. Either trifluridine or vidarabine ophthalmic drops (in conjunction with i.v. acyclovir in neonates) are recommended (Sudesh and Laibson, 1999). A randomized, placebo-controlled trial has demonstrated that long-term suppressive oral acyclovir therapy is effective in reducing the rate of recurrences (Herpetic Eye Disease Study Group, 2000). Continuous suppressive therapy is preferred rather than intermittent dosing and may best be administered by daily dosing with valacyclovir (Simmons, 2002).

5.3. Genital HSV infections

Although HSV-2 most commonly causes genital herpes, the frequency of disease due to HSV-1 is increasing (Ashley and Wald, 1999; Lafferty, 2002). Vesicles or ulcers may be present on the perineum, labia majora, and labia minora in women, and on the shaft of the penis and glans in men. Perianal lesions may also be seen. Primary infection may be associated with aseptic meningitis and pharyngitis, especially in women (Ashley and Wald, 1999). Most patients with suspected first episode genital herpes should be started on antiviral therapy while awaiting laboratory confirmation. Available therapies include i.v. and oral acyclovir, famciclovir, and valacyclovir (reviewed in Centers for Disease Control and Prevention, 2002; Corey, 2002; Lafferty, 2002; Patel, 2002). Intravenous acyclovir is reserved for those requiring hospitalization. The efficacy of the oral agents is similar; famciclovir and valacyclovir offer the advantage of less frequent dosing. These therapies decrease the duration

of illness and viral shedding but do not alter the frequency or severity of subsequent recurrences. Topical acyclovir is not recommended.

Patients with genital HSV-2 infection usually have recurrences which may produce recognizable symptoms, unrecognized symptoms or be asymptomatic for many years after their first episode (Ashley and Wald, 1999). Recurrences can be treated with oral acyclovir (Wald et al., 2002), famciclovir (Sacks et al., 1996), and valacyclovir (Spruance et al., 1996). Treatment reduces the duration of viral shedding and time to lesion healing. For individuals who suffer frequent or severe recurrences, or who would benefit from reducing the frequency of recurrences, chronic (daily) suppressive therapy is more appropriate than episodic therapy. Recurrences may be reduced by up to 75% and symptoms are milder (Straus et al., 1984; Reitano et al., 1998; Mertz et al., 1997). Recent studies also show that asymptomatic shedding is decreased (Wald et al., 1996, 1997) and transmission to a susceptible partner was reduced in one study evaluating valacyclovir (Corey et al., 2002).

5.4. Cutaneous infections

Herpetic whitlow, infection of the pulp of the finger, results from digital contamination with contaminated oral or genital secretions (Nikkels and Pierard, 2002). Young children develop *herpetic whitlow* as a result of autoinoculation of HSV-1 during primary oral infection. Health care professionals are another group at high risk for *herpetic whitlow*. Additional trauma to the digit (e.g. opening of the vesicular lesions) should be avoided. Data on antiviral treatment are limited but patients with severe disease may benefit from treatment. Rates of recurrences are lower than those observed with oral or genital disease.

HSV gladiatorum refers to skin infections among athletes participating in contact sports, such as wrestling (Belongia et al., 1991). Since primary infections and recurrences exclude athletes from continued participation, prophylactic use of antivirals during the sports season has been recommended (Anderson, 1999).

HSV infections of damaged skin may be particularly severe in individuals with burns and atopic dermatitis. *Eczema herpeticum* is the term applied to serious, widespread HSV infections in patients with eczema (Nikkels and Pierard, 2002). Systemic acyclovir therapy is indicated for both primary infections and recurrences. Some individuals with frequent severe recurrences benefit from long-term suppressive therapy.

5.5. HSV infections of the central nervous system

In the Western world, HSV is the most common cause of severe sporadic encephalitis (Whitley and Lakeman, 1995). Beyond the neonatal period, more than 95% of cases are caused by HSV-1. Encephalitis occurs most commonly as a result of reactivation, rather than primary infection. Any individual with suspected HSV encephalitis should be treated promptly with i.v. acyclovir while diagnostic procedures are pursued. PCR is the diagnostic method of choice. The mortality among untreated patients exceeds 70%. Characteristics associated with poor outcome include the development of coma, age more than 30 years, and clinical encephalitis for more than 4 days before initiation of therapy (Whitley and Lakeman, 1995). Even with appropriate antiviral therapy, progressive neurologic impairment may result (Whitley and Lakeman, 1995). Reactivations of HSV in the brain are hypothesized to contribute to this progressive damage. The efficacy of a prolonged course of suppressive valacyclovir following initial i.v. acyclovir treatment of HSV encephalitis is being evaluated in a randomized, double-blind, placebo-controlled trial in adults.

5.6. Neonatal HSV infections

HSV infection of the newborn is a devastating disease with a high mortality if untreated. In the neonate, 60–70% of HSV infections are due to HSV-2 and the remainder HSV-1 (Kimberlin et al., 2001a). The neonate most often acquires the infection in the intrapartum period via viral shedding from the female genital tract. Other routes of transmission include transplacental passage of the virus and contact spread from an infected caregiver in the postpartum period. The three major categories of neonatal HSV infection which determine prognosis are skin, eye, and mouth (SEM) disease only, CNS disease, and disseminated disease involving multiple organs, including the liver and lungs (Kimberlin et al., 2001a; Kimberlin, 2001). High dose i.v. acyclovir is the treatment of choice for all neonatal HSV infections although the outcome, especially of CNS disease, remains unacceptably poor (Kimberlin et al., 2001b). A phase I/II study concluded that administration of oral acyclovir suppressive therapy after neonatal SEM disease prevented cutaneous recurrences (Kimberlin et al., 1996). A larger phase III study is in progress to evaluate the effect of such therapy on neurologic outcomes.

5.7. HSV infections in the immunocompromised host

All of the above clinical manifestations of HSV disease can be seen in immunocompromised hosts, especially those with impairments in cellular immune responses. Mucocutaneous disease among these patients may be protracted and slow to respond to antiviral therapy (Stewart et al., 1995). Viremic spread of HSV may lead to infection of multiple visceral organs. Additionally, the risk of selecting for acyclovir-resistant HSV isolates during long-term therapy is a concern. Oral therapies (acyclovir, famciclovir, or valacyclovir) or i.v. acyclovir, depending on the severity of disease, are indicated. If disease is recalcitrant to i.v. acyclovir, then foscarnet should be substituted and antiviral susceptibilities determined to guide further therapy (Chilukuri and Rosen, 2003).

6. Specific antiviral agents (Table 1)

6.1. Acyclovir and valacyclovir

The nucleoside analog acyclovir specifically targets herpes virus-infected cells because the viral thymidine kinase (TK) phosphorylates acyclovir to its monophosphate form. Cellular kinases then perform subsequent phosphorylations, yielding biologically active acyclovir triphosphate. Acyclovir triphosphate selectively inhibits viral DNA polymerase, preventing further elongation of the viral DNA chain. HSV develops resistance to acyclovir predominantly as a result of alterations in viral TKs and less frequently from mutations in the viral DNA polymerase (Kimberlin et al., 1995). To date, disease due to resistant viruses is almost exclusively a problem only in the immunocompromised (Bacon et al., 2003; Field, 2001; Shin et al., 2001) (Table 1).

The bioavailability of oral acyclovir is only 10–20%; thus, subsequent improvements have targeted better absorption. Valacyclovir, the L-valine ester of acyclovir, is well absorbed (50%) and rapidly converted to acyclovir in the liver (Tyring et al., 2002). Valacyclovir is only available as caplets. Acyclovir is available as an i.v. preparation, a suspension for oral use, capsules, tablets, and a 5% ointment for topical use.

6.2. Penciclovir and famciclovir

The mechanism of action of the guanosine analog penciclovir is similar to that of acyclovir. Although penciclovir triphosphate is 100-fold less potent in inhibiting viral DNA polymerase than acyclovir triphosphate, it achieves higher intracellular concentrations and has a longer half-life in HSV-infected cells (Cirelli et al., 1996). Currently, penciclovir is only available as a 1% topical cream. Studies evaluating the safety and efficacy of i.v. penciclovir are ongoing.

Famciclovir, a diacetyl ester prodrug of penciclovir, is well absorbed (70%) from the gastrointestinal tract (Cirelli et al., 1996). Famciclovir is only available as tablets.

6.3. Trifluridine

Trifluridine, a pyrimidine nucleoside analog, also has a similar mechanism of action (Carmine et al., 1982). Trifluridine triphosphate inhibits viral and cellular DNA polymerases at relatively low concentrations, and thus is too toxic for systemic use. Trifluridine is only available as a 1% solution for treatment of HSV ocular infections.

6.4. Vidarabine

Vidarabine (Ara-A), one of the earliest effective HSV drugs, is an adenine analog that is phosphorylated by cellular kinases to vidarabine triphosphate, which competitively inhibits viral, and to a lesser extent, cellular DNA polymerases. Intravenous vidarabine is no longer manufactured in the United States because i.v. acyclovir has greater safety and efficacy. Vidarabine is available as a 3% ointment for treatment of HSV ocular infections.

6.5. Foscarnet

Foscarnet directly inhibits the viral DNA polymerase and does not require phosphorylation by viral TK (Field, 2001; Morfin and Thouvenot, 2003; Chilukuri and Rosen, 2003). It is active against acyclovir-resistant, TK-deficient HSV isolates. Resistance to foscarnet is rare and arises via mutations in the viral DNA polymerase (Morfin and Thouvenot, 2003; Chilukuri and Rosen, 2003). Foscarnet is only available as an i.v. preparation. Its significant toxicities limit its HSV use to treatment of acyclovir-resistant infections.

6.6. Cidofovir

Cidofovir is an acyclic nucleoside 5′-monophosphate that is phosphorylated by host cell kinases to a biologically active intracellular metabolite which selectively inhibits the viral DNA polymerase (Morfin and Thouvenot, 2003; Chilukuri and Rosen, 2003). Because cidofovir is not dependent on viral TK for activation, it is also active against TK-deficient HSV isolates. Resistance to cidofovir is rare and arises via mutations in the viral DNA polymerase gene. The half-life of the active form is long, permitting once weekly dosing. Cidofovir is only available as an i.v. preparation which has substantial nephrotoxicity (Morfin and Thouvenot, 2003; Chilukuri and Rosen, 2003). A 1% gel may be prepared from the intravenous form for topical use (Leung and Sacks, 2000). Use of cidofovir is restricted to the treatment of HSV disease due to isolates that are resistant to acyclovir and foscarnet (Chilukuri and Rosen, 2003).

6.7. Docosanol

Docosanol (a saturated 22-carbon aliphatic alcohol) appears to inhibit fusion between the host cell plasma membrane and the HSV envelope, blocking viral entry (Pope et al., 1998). Docosanol is available over-the-counter as a 10% topical cream for the treatment of recurrent *herpes labialis*.

7. Emerging therapies

Resiquimod is a topical immune response modifier that is being evaluated in randomized, double-blind, placebo-controlled clinical studies for its safety and efficacy in delaying recurrences of genital herpes and *herpes labialis* (Bernstein, 2001).

Topical microbicides, products to be used intravaginally by women for protection against genital herpes and other sexually transmitted infections, are being evaluated in preclinical trials.

Table 1
Therapeutic agents

Oral acyclovir	
Standard dosage	First episode genital herpes: 200 mg five times per day or 400 mg three times per day for 7–10 days. Recurrent genital herpes: 200 mg five times per day or 400 mg three times per day or 800 mg b.i.d. for 5 days. Chronic suppressive therapy for genital herpes: 400 mg b.i.d. Episodic mucocutaneous HSV infection in HIV-infected patients: 400 mg three times per day or 200 mg five times per day for 5–10 days. Chronic suppressive therapy for HSV infections in HIV-infected patients: 400–800 mg b.i.d. or t.i.d. Primary gingivostomatitis in children: 15 mg/kg/dose five times per day for 7 days.
Contraindications	Hypersensitivity to acyclovir or valacyclovir. Dose adjustments are required for individuals with renal insufficiency.
Main drug interactions	May decrease serum levels of fosphenytoin, phenytoin, and valproic acid. Monitor drug levels of interacting drugs. Concurrent use with mycophenolate mofetil may result in an increase in plasma concentrations of acyclovir. Use caution when administering acyclovir to patients receiving potentially nephrotoxic drugs.
Main side effects	Nausea, vomiting, headache, diarrhea, and malaise. Dizziness, confusion, lethargy, agitation, and seizures are uncommon but may be observed in elderly patients. Transient renal and hematologic abnormalities may occur. Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), which has resulted in death, rarely has been reported in immunocompromised patients receiving acyclovir.
Special points	Acyclovir has been the standard antiviral therapy for HSV infections for more than 15 years.
Cost effectiveness	The cost of treatment for first episode genital herpes (200 mg five times per day for 10 days) varies from $17 (generic drug) to $67 (name brand drug).
Valacyclovir	
Standard dosage	First episode genital herpes: 1 g b.i.d. for 7–10 days. Recurrent genital herpes: 0.5 g b.i.d. for 3–5 days or 1 g daily for 5 days. Chronic suppressive therapy for genital herpes: 0.5–1 g daily (1 g recommended). Episodic mucocutaneous HSV infection in HIV-infected patients: 1 g b.i.d. for 5–10 days. Chronic suppressive therapy for HSV infections in HIV-infected patients: 500 mg b.i.d. *Herpes labialis*: 2 g twice daily for 1 day; separate doses by 12 h.
Contraindications	Same as for oral acyclovir.
Main drug interactions	Renal insufficiency and CNS symptoms have been reported in patients with renal impairment who have received valacyclovir in combination with other nephrotoxic drugs.
Main side effects	Nausea, vomiting, and headache. TTP/HUS rarely has been reported in immunocompromised patients receiving high doses of valacyclovir (8 g per day).
Special points	A preliminary pharmacokinetic evaluation in immunocompromised children has been reported (Nadal et al., 2002).
Cost effectiveness	The cost of treatment of primary genital herpes (1 g b.i.d. for 10 days) is $140. More expensive than acyclovir but less frequent dosing may improve compliance.
Famciclovir	
Standard dosage	First episode genital herpes: 250 mg t.i.d. for 7–10 days. Recurrent genital herpes: 125 mg b.i.d. for 5 days. Chronic suppressive therapy for genital herpes: 250 mg b.i.d. Recurrent mucocutaneous HSV infections in HIV-infected patients: 500 mg b.i.d. for 5–10 days. Chronic suppressive therapy for HSV infections in HIV-infected patients: 500 mg b.i.d.
Contraindications	Hypersensitivity to famciclovir or penciclovir. Dosage adjustments are required for individuals with renal insufficiency.
Main drug interactions	Probenicid and other drugs that are eliminated by active tubular secretion may increase penciclovir concentrations. The conversion of 6-deoxy penciclovir to penciclovir is catalyzed by aldehyde oxidase. Interactions with other drugs metabolized by this enzyme could potentially occur.
Main side effects	Headache, nausea, vomiting, diarrhea, fatigue, paresthesia, and pruritis can occur.
Special points	The pharmacokinetics of famciclovir or penciclovir have not been evaluated in patients <18 years of age.
Cost effectiveness	The cost of treatment of primary genital herpes (250 mg t.i.d. for 10 days) is $110. More expensive than acyclovir but less frequent dosing may improve compliance.
Intravenous acyclovir	
Standard dosage	Mucocutaneous HSV infections in immunocompromised patients: Adults and adolescents ≥12 years of age: 5 mg/kg/dose every 8 h for at least 7 days. Children <12 years of age: 10 mg/kg/dose every 8 h for at least 7 days. Severe initial clinical episodes of genital herpes: Adults and adolescents ≥12 years of age: 5 mg/kg/dose every 8 h for 5 days. Herpes simplex encephalitis: Adults and adolescents ≥12 years of age:

Table 1 (*Continued*)

	10 mg/kg/dose every 8 h for 14–21 days. Children 3 months to 12 years of age: 20 mg/kg/dose every 8 h for 14–21 days. Neonates and infants <3 months of age: 20 mg/kg/dose every 8 h for 21 days. Neonatal HSV infections (birth to 3 months): 20 mg/kg/dose every 8 h. (14 days for SEM disease); (21 days for disseminated and CNS disease).
Contraindications	Same as for oral acyclovir.
Main drug interactions	Same as for oral acyclovir.
Main side effects	Same as for oral acyclovir. When administering doses of 10 mg/kg/dose every 8 h or greater, the patient should be well hydrated to avoid renal tubular crystallization of the drug. Great caution is required when administering i.v. acyclovir to patients with renal failure who are on dialysis. Even with dose reductions, these patients may develop CNS adverse effects. Phlebitis has also been reported at the injection site.
Special points	Intravenous infusions should be administered over at least 1 h to reduce the risk of renal tubular damage. Acyclovir is the safest drug administered i.v. for treatment of HSV infections. PCR evaluation of CSF prior to discontinuing therapy for HSV encephalitis is recommended.
Cost effectiveness	The cost of treatment (5 mg/kg/dose every 8 h for 7 days) for an average adult with normal renal function is $830. Costs of placing and maintaining the i.v. catheter, nursing care, and laboratory tests are not included.
Foscarnet	
Standard dosage	Indicated for use only in patients with acyclovir-resistant HSV infections. Dosage is 40 mg/kg (administered as a minimum 1 h i.v. infusion) every 8 h for 2–3 weeks or until all lesions are healed. To establish diuresis, 750–1000 ml of normal saline or 5% dextrose solution should be given prior to the first infusion of foscarnet. After the first dose, the hydration fluid should be administered concurrently with each infusion of foscarnet.
Contraindications	Hypersensitivity to foscarnet. Renal insufficiency is a relative contraindication because of the nephrotoxicity of foscarnet.
Main drug interactions	Avoid other nephrotoxic drugs (e.g. aminoglycosides, amphotericin B, cidofovir, i.v. pentamidine, vancomycin, and non-steroidal anti-inflammatory agents).
Main side effects	Renal impairment is the major toxicity. Electrolyte abnormalities, including hypocalcemia, hypophosphatemia, hyperphosphatemia, hypomagnesemia, and hypokalemia, can occur. Seizures, anemia, fever, headache, nausea, vomiting, and diarrhea have been reported.
Special points	Individualize dosing according to the patient's renal function. Determine electrolytes (calcium, magnesium, phosphorus, and potassium) and creatinine clearance at baseline and at least two to three times per week during therapy. Discontinue if creatinine clearance drops below 0.4 ml/min/kg.
Cost effectiveness	For an average-sized adult with normal renal function, the cost of treatment for 7 days is $715. Costs of placing and maintaining the i.v. catheter, hydration fluids, laboratory tests, and nursing care are not included.
Cidofovir	
Standard dosage	Indicated for the treatment of acyclovir-resistant and foscarnet-resistant HSV infections. It is supplied as a 75 mg/ml solution for i.v. infusion and should be diluted in 100 ml normal saline and infused over 1 h. Induction dose: 5 mg/kg once weekly for 2 consecutive weeks. Maintenance dose: 5 mg/kg once every 2 weeks; reduce to 3 mg/kg if serum creatinine increases 0.3–0.4 mg/dl above baseline. Discontinue if serum creatinine increases ≥0.5 mg/dl above baseline or if >3+ proteinuria develops. Prehydrate with normal saline and administer probenicid prior to cidofovir infusion. Administer probenicid 8 h after the cidofovir infusion has ended. Patients who can tolerate the fluid load should receive a second liter of normal saline either during or after each dose of cidofovir.
Contraindications	Serum creatinine >1.5 mg/dl or calculated creatinine clearance ≤55 ml/min, or a urine protein ≥100 mg/dl (equivalent to ≥2+ proteinuria). Discontinue all medications with nephrotoxic potential at least 7 days prior to initiating cidofovir. Hypersensitivity to cidofovir, probenicid, or other sulfa-containing medications.
Main drug interactions	Other nephrotoxic drugs are contraindicated. Probenicid interacts with the metabolism or renal tubular secretion of many drugs and, therefore, all concomitant drugs should be carefully assessed.
Main side effects	Dose-dependent nephrotoxicity is the major toxicity. Cases of acute renal failure resulting in dialysis and/or contributing to death have occurred with only one or two doses. Neutropenia, decreased intraocular pressure, ocular hypotony, uveitis, iritis, and metabolic acidosis can occur.
Special points	Monitor serum creatinine, urine protein, and white blood cell count with differential before each dose. Intraocular pressure, visual acuity, and ocular symptoms should be monitored periodically. In animal studies, cidofovir was carcinogenic, teratogenic, and caused hypospermia. Women should use effective contraception during and 1 month after therapy. Men should use barrier contraception during and 3 months after therapy.
Cost effectiveness	The cost for a single dose of cidofovir for an average-sized adult with normal renal function is $850. Costs of placing and maintaining the i.v. catheter, saline infusions, probenicid, nursing care, and laboratory tests for monitoring renal function and blood cell counts are not included.
Acyclovir ointment	
Standard dosage	Indicated in the management of initial genital herpes and in limited non-life-threatening mucocutaneous HSV infections. Apply a sufficient quantity to cover all lesions using a finger cot or rubber glove every 3 h, six times per day for 7 days. Use an approximately 1/2 in. ribbon of ointment per 4 $in.^2$ of surface area.

Table 1 (*Continued*)

Contraindications	Hypersensitivity to acyclovir or any ingredient in the product.
Main drug interactions	None because transcutaneous absorption is minimal.
Main side effects	Pain, edema, pruritis, or a rash at the application site.
Special points	Avoid direct application near the eyes.
Cost effectiveness	A 3 g tube costs $28.
Penciclovir	
Standard dosage	Indicated for the treatment of recurrent *herpes labialis* in individuals ≥18 years of age. Dosage: apply every 2 h while awake for 4 days.
Contraindications	Hypersensitivity to penciclovir, famciclovir, or any ingredient in the product.
Main drug interactions	None because systemic absorption after topical application is negligible.
Main side effects	Potential local reactions include an erythematous rash, pain, pruritis, and taste perversion. Headache can also occur.
Special points	Effectiveness has not been established in children or immunocompromised patients. Avoid direct application to the mucous membranes or near the eyes.
Cost effectiveness	A 1.5 g tube costs $25.
Docosanol	
Standard dosage	Indicated for the treatment of recurrent *herpes labialis* in individuals ≥12 years of age. Dosage: apply five times daily until healed.
Contraindications	Hypersensitivity to docosanol or any ingredient in the product.
Main drug interactions	None because systemic absorption after topical application is negligible.
Main side effects	Headache and application site reactions, such as pain, pruritis, and an erythematous rash.
Special points	Avoid direct application to the mucous membranes or near the eyes. Discontinue use and consult a physician if the lesion worsens or is not healed within 10 days. To avoid the spread of infection, do not share this product with others.
Cost effectiveness	A 2 g tube costs $14.
Trifluridine	
Standard dosage	Indicated for the treatment of primary keratoconjunctivitis and recurrent epithelial keratitis due to HSV. For individuals ≥6 years of age: one drop every 2 h while awake; maximum nine drops per day, not recommended for longer than 21 days. After re-epithelialization, one drop every 4 h for an additional 7 days (at least five drops per day). Re-evaluate if no improvement in 7 days or incomplete re-epithelialization in 14 days.
Contraindications	Hypersensitivity or chemical intolerance to trifluridine.
Main drug interactions	None because systemic absorption after intraocular administration is negligible.
Main side effects	Mild, transient ocular burning upon instillation, and palpebral edema. Increased intraocular pressure can occur.
Special points	Individuals should be followed closely by an ophthalmologist while receiving treatment.
Cost effectiveness	The cost of a 7.5 ml bottle varies from $90 to $100.
Vidarabine	
Standard dosage	Indicated for the treatment of primary keratoconjunctivitis and recurrent epithelial keratitis due to HSV. For individuals ≥2 years of age: 1/2 in. in affected eye(s) every 3 h while awake (maximum five times daily) until re-epithelialization. After re-epithelialization, treat for an additional 7 days at a lower dose, such as b.i.d. Re-evaluate if no improvement in 7 days.
Contraindications	Hypersensitivity or chemical intolerance to vidarabine.
Main drug interactions	None because systemic absorption after intraocular administration is negligible.
Main side effects	Ocular burning, photophobia, lacrimation, and a foreign body sensation.
Special points	Individuals should be followed closely by an ophthalmologist while receiving treatment.
Cost effectiveness	A 3.5 g tube costs $28.

Cost estimates are based on Cohen (2003).

8. Vaccine development

The development of HSV vaccines has been challenging because the viruses establish latency and reactivations occur in the presence of humoral and cell-mediated immunity (Bernstein and Stanberry, 1999).

Potential goals for HSV vaccines include:

(1) prevention or amelioration of disease with or without partial protection against infection;
(2) protection of the sensory ganglia from latent infection;
(3) prevention of recurrences in individuals who are already latently infected with HSV.

The HSV vaccines that have been studied to the greatest extent are subunit glycoprotein constructs. A recombinant truncated gD2 (glycoprotein D of HSV-2) combined with alum and the adjuvant MPL (3-de-*O*-acylated monophosphoryl lipid A) vaccine (GlaxoSmithKline) is being evaluated in phase III clinical trials for the prevention of genital herpes in women who are seronegative for both HSV-1 and HSV-2 (Stanberry et al., 2002).

Alternative approaches for HSV vaccines include genetically attenuated or replication-impaired HSVs, DNA vaccines, and vectored vaccines.

9. Summary

Many infections with herpes simplex viruses type 1 and type 2 (HSV-1, HSV-2) are asymptomatic or unrecognized.

Primary infection leads to a persistent (latent) lifetime infection which can reactivate to cause recurrent disease or asymptomatic shedding of the virus at the portal of entry. Infection can lead to a variety of skin and mucosal diseases, the most common being genital and orolabial disease. The suggested options for treatment of primary orolabial or genital herpes infections include oral acyclovir, valacyclovir, and famciclovir. The latter two are better absorbed than acyclovir and, therefore, can be given less frequently, increasing compliance. Treatment with these latter two drugs, however, is more expensive. Treatment of recurrent disease with these same agents soon after signs and symptoms begin offers moderate benefits while daily suppressive therapy can effectively decrease clinical recurrences by >70%. Chronic daily suppressive therapy has the additional benefit of decreasing viral shedding and probable transmission. More serious HSV diseases, such as neonatal herpes and herpes encephalitis, should always be treated with i.v. acyclovir as quickly as possible. Treatment options for viruses resistant to the above drugs include foscarnet and cidofovir.

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