Herpes Simplex Virus in Children

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Opinion statement

- Herpes simplex virus (HSV) infections are ubiquitous. Children are infected with HSV resulting in totally asymptomatic acquisition to life-threatening disease. Therapy of HSV diseases of children can be considered according to severity and time of acquisition [1•].
- Neonatal herpes simplex virus infections take one of three forms—disease localized to skin, eye, or mouth (SEM), encephalitis, or multiorgan disseminated disease. Treatment consists of intravenous (IV) administration of acyclovir. Supportive care for patients with life-threatening disease is an integral component of patient management.
- Mucocutaneous HSV infections in the immunocompromised host can be treated with either intravenous acyclovir or one of the orally bioavailable antiviral therapies. For hospitalized patients, therapy consists of IV acyclovir at 5 mg/kg every 8 hours for 7 to 14 days. For ambulatory patients, therapy is tailored according to age. For children less than 12 years of age, oral acyclovir is administered at a dosage of 20 mg/kg every eight hours. Although no controlled studies have been performed with valaciclovir or famciclovir, the pharmacokinetics of these medications would suggest superiority over acyclovir. Dosage recommendations have not been established for young children. For postpubertal children, dosage should mirror that of adults. Valaciclovir is administered at 500 mg twice daily. Famciclovir is administered at 125 mg three times daily.
- Herpes simplex keratoconjunctivitis is treated with topical triflurothymidine. Two drops are applied to the infected eye five times daily until resolved. Recurrences are managed in a similar manner. Some physicians administer oral acyclovir at the doses noted above in order to prevent frequent recurrences.
- Genital HSV infections can be treated with acyclovir, valaciclovir, or famciclovir. Episodic treatment of recurrent episodes is usually not necessary in childhood. Importantly, all data on the use of these compounds for these conditions have been generated in adults.
- Physician judgment is required for the management of recurrent herpes labialis, erythema multiforme, and herpes gladitorum. No controlled studies have been performed in children, although experience with acyclovir, valaciclovir, and famciclovir have resulted in their use.

Introduction

Herpes simplex virus (HSV) infections have been recognized since ancient Greek times. In fact, *herpes*, in Greek, means to creep or crawl, as is characteristic of the resulting skin lesions. This virus is responsible for a variety of clinical diseases, many of which require antiviral therapy because of associated mortality or morbidity. With a predilection to infect neuronal tissue, HSV establishes latency and can be reactivated with the proper provocative stimulus, *ie,* fever, exposure to ultraviolet light, stress, menses, and others [2].

Although many children are infected with HSV, few actually develop disease. Indeed, as socioeconomic condi-

tions improve, acquisition of HSV infection is occurring at increasing later ages in life. Initial acquisition of infection is the consequence of direct and intimate contact with an infected individual. Thus, from a pathogenesis perspective, neonatal HSV infection is usually the consequence of exposure of the fetus to infected maternal genital secretions. Herpes gladiatorum results from skin to saliva contact among wrestlers. Genital HSV infections result either from genital to genital or oral to genital contact. By adolescence, approximately 20% of Americans are infected by HSV type 1 (HSV-1). Infection with HSV type 2 (HSV-2) begins with the onset of sexual activity in most cases.

Life-threatening disease attributed to HSV occurs in the newborn and with herpes simplex encephalitis. Neonatal HSV infection occurs at an incidence of 1 per 3500 to 5000 live births, although in some areas it is increasing in frequency. As noted, disease presents as one of three forms— localized to skin, eye, or mouth (SEM), encephalitis, or multiorgan disseminated disease. The mortality in the absence of therapy for each form respectively is 0%, 70%, and 85%. Attributable morbidity, again in the absence of therapy, is 5%, 90%, and 50% of survivors [3••,4, Class I]. Antiviral therapy has significantly improved these outcome data such that only 5% and 25% of children with encephalitis and disseminated disease succumb, and over 50% of survivors develop normally [5••,6•, Class I]. There are approximately 2500 cases of HSV encephalitis annually in the US, and at least one third of these occur in children. Treatment has reduced mortality to approximately 25%, and about 50% of survivors return to normal function. Rigorous controlled clinical trials have established the value of antiviral therapy for these indications [7,8, Class I].

Mucocutaneous and ocular HSV infections are a significant cause of morbidity. There is a broad spectrum of disease, as noted previously, involving the eye, mouth, skin (primarily the immunocompromised host), and genital tract. Controlled clinical trials that provide evidence of therapeutic use of antiviral drugs in children are limited for most of these indications. Regardless, many physicians often elect off label use of one of the agents noted in this article [9, Class III].

Acyclovir and its related compounds—valaciclovir and famciclovir—are the mainstay of antiviral therapy of HSV infections. Acyclovir is available in topical, oral, and intravenous (IV) formulations for the treatment of HSV infections. Current use selects either the oral or intravenous formulation for treatment. Acyclovir is selectively phosphorylated by HSV thymidine kinase to acyclovir-monophosphate. Cellular kinases then metabolize the drug to its triphosphate derivative. Acyclovir triphosphate is both a viral DNA chain terminator as well as competitive inhibitor of viral DNA polymerase, thereby conferring a high degree of specificity to its mechanism of action. Acyclovir triphosphate is not incorporated into host cell or viral DNA. It is licensed for the treatment of HSV infections of the newborn, central nervous system (CNS), and genital herpes, among other herpesvirus infections, as noted elsewhere in this article. The oral bioavailability of acyclovir is approximately 20%. The kidney clears the drug; thus, in the presence of renal impairment, dosage adjustment is required [2,9].

Valaciclovir is the l-valine ester prodrug of acyclovir. The valine ester is cleaved from the parent compound on absorption from the gastrointestinal tract, leaving free acyclovir in the blood. The resulting acyclovir is metabolized by infected cells in the fashion noted previously. The oral bioavailability of valaciclovir is approximately 70%. As would be expected, valaciclovir is metabolized to acyclovir, the primary route of clearance is by the kidney. Valaciclovir is licensed for the treatment of genital HSV infections as well as other herpesvirus infections [10–13, Class I]

Famciclovir is the di-ester derivative of penciclovir. Penciclovir has a very low oral bioavailability (less than 5%). Famciclovir has one ester derivative cleaved on absorption from the gastrointestinal tract and the other by the liver, resulting in penciclovir in the blood. The resulting oral bioavailability is about 85%. Penciclovir has a subtly different mechanism of action as compared to acyclovir. This medication has a terminal 3′-hydroxyl group that can be phosphorylated. Thus, it is a competitive inhibitor of HSV DNA polymerase, but not an obligatory chain terminator. In fact, it can be incorporated into viral DNA. This finding may account for recognized carcinogenicity in preclinical toxicology studies. The kidney clears the drug. Famciclovir is licensed for the treatment of genital HSV infections, as well as infections caused by other members of the herpesvirus family [14,15, Class II]

An additional compound is available for the treatment of HSV infections resistant to the aforementioned antiviral medications, namely foscarnet. It is a pyrophosphate analogue that binds directly to viral DNA polymerase. It is reserved for the immunocompromised host with resistant infection.

Of note, the pharmacodynamics have established the superiority of valaciclovir and famciclovir over acyclovir for the treatment of HSV diseases in adults. Neither drug exists in a pediatric formulation. Furthermore, neither drug has been studied in a pediatric population. However, many physicians elect to substitute these medications for acyclovir in spite of the lack of evidence based studies.

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Treatment

- The treatment of HSV infections should be guided by disease severity. For life-threatening infections, the only available therapeutic is acyclovir administered IV. Such infections include neonatal HSV disease, herpes simplex encephalitis, and, sometimes, disseminated HSV infections in the immunocompromised host or complications of first episode genital HSV infections (*ie,* meningitis). For HSV infections that induce morbidity, an oral therapeutic can be selected, including acyclovir, valaciclovir, or famciclovir. Topical therapy should only be used to treat ocular infections.

Neonatal herpes simplex virus infection therapy

- The aims of therapy are to 1) decrease mortality associated with encephalitis and disseminated, multi-organ disease; 2) improve morbidity for all three forms of disease; and 3) prevent progression from SEM disease to one of the more serious forms of infection, namely either encephalitis or disseminated disease.

Acyclovir

Standard dosage	20 mg/kg IV every 8 hours (total of 60 mg/kg daily) for 14 days if the child has SEM disease or 21 days if encephalitis or multiorgan involvement is present. The strength of this evidence resides in Class I studies.
Contraindications	Acyclovir is one of the safest medications licensed to date. There are no known contraindications to this medication.
Main drug interactions	None reported.
Main side effects	Side effects are a function of the route of administration. For any route of administration, acyclovir is generally well tolerated. Gastrointestinal disturbances, headache, and local irritation can occur. Given IV, the drug may cause phlebitis and inflammation at sites of infusion or extravasation. Intravenous acyclovir may also cause reversible renal dysfunction, because of crystalline nephropathy; rapid infusion, dehydration, renal insufficiency, and high dosage increase the risk. Intravenous and rarely oral acyclovir has been associated with encephalopathy, including tremors, hallucinations, seizures, and coma. High doses of acyclovir cause testicular atrophy in rats, and high concentrations cause chromosomal damage in vitro, but no adverse effects on sperm production or cytogenetic alterations in peripheral blood lymphocytes have been detected in patients who have taken the drug orally for more than 10 years to suppress recurrent genital herpes. The manufacturer recommends stopping the drug during pregnancy, but a pregnancy registry found no unusual or excess incidence of birth defects in the offspring of more than 600 women who took acyclovir during the first trimester.
Special points	Dosage adjustment is required in the presence of renal impairment. The dosage modification appears in Table 1. There is no role for valacyclovir or famciclovir in the management of neonatal HSV infection. Furthermore, the safety and efficacy of oral acyclovir management following intravenous therapy is not established at this time.
Cost/cost effectiveness	The cost of acyclovir is $242.04.

Herpes simplex encephalitis therapy

- The aims of therapy of herpes simplex encephalitis are to decrease mortality and improve morbidity.

Table 1. Dosage adjustment for intravenous acyclovir in patients with impaired renal function [16]

Creatine clearance (mL/minute/1.73 m^2)	Standard dose, %	Dosing interval, *h*
greater than 50	100	8
25 to 50	100	12
10 to 25	100	24
0 to 10*	50	24

*Administered after hemodialysis.

Acyclovir

Standard dosage 10 to 15 mg/kg IV every 8 hours for 14 to 21 days. Of note, the dosage is lower for patients with encephalitis outside the newborn period because of the potential for nephrotoxicity. The evidence for its use in the management of this disease is Class I.

Contraindications Acyclovir is one of the safest medications licensed to date. There are no known contraindications to this medication.

Main drug interactions None reported.

Main side effects Side effects are a function of the route of administration. For any route of administration, acyclovir is generally well tolerated. Gastrointestinal disturbances, headache, and local irritation can occur. Given IV, the drug may cause phlebitis and inflammation at sites of infusion or extravasation. Intravenous acyclovir may also cause reversible renal dysfunction, because of crystalline nephropathy; rapid infusion, dehydration, renal insufficiency, and high dosage increase the risk. Intravenous and rarely oral acyclovir has been associated with encephalopathy, including tremors, hallucinations, seizures, and coma.

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Cost/cost effectiveness The cost of acyclovir is $2380.13.

Mucocutaneous herpes simplex infections in the immunocompromised host therapy

- The aims of therapy are to accelerate the events of healing of mucocutaneous lesions and to prevent spread to other organs (*ie,* lung, esophagus, or gastrointestinal tract).

Acyclovir

Standard dosage 10 to 15 mg/kg IV every 8 hours for hospitalized patients for a period of 7 to 10 days.

For children with mild lesions who can be managed on an ambulatory care basis oral acyclovir can be administered at a dosage of 20 mg/kg every 8 hours per orum for 7 to 10 days. The maximum dose would be 1 g daily.

Evidence for the use of acyclovir in these circumstances is predicated on Class I studies in adults and Class II studies in children.

Contraindications Acyclovir is one of the safest medications licensed to date. There are no known contraindications to this medication.

Main drug interactions None reported.

Main side effects For IV administration, the drug may cause phlebitis and inflammation at sites of infusion or extravasation. Intravenous acyclovir may also cause reversible renal dysfunction, because of crystalline nephropathy; rapid infusion, dehydration, renal insufficiency, and high dosage increase the risk. Intravenous and rarely oral acyclovir has been associated with encephalopathy, including tremors, hallucinations, seizures, and coma.

For oral therapy, nausea and vomiting occur at low frequency. Other notable side effects have not been reported.

Cost/cost effectiveness The cost for acyclovir 5 mg/kg is $685.85.

Valaciclovir

Standard dosage 500 to 1000 mg orally twice daily for 7 to 10 days. The evidence is predicated on Class II studies.

Contraindications None known.

Main drug interaction None reported.

Main side effects In addition to nausea and vomiting, a thrombotic thrombocytopenic purpura syndrome has been reported in patients with HIV infection at doses of 6 g daily.

Cost/cost effectiveness The cost for valaciclovir is $71.62.

Famciclovir

Standard dosage 250 mg per orum three times daily for 7 to 10 days. The evidence is based on Class II studies.

Contraindications None known.

Main drug interactions None known.

Main side effects The principle side effects are nausea and vomiting at very low frequency.

Cost/cost effectiveness The cost for famciclovir is $106.53.

Herpes simplex gingivostomatitis therapy

- The goal of therapy would be to accelerate defervescence, resolution of pain, and accelerate oral intake in order to avoid hospitalization for dehydration.

Acyclovir

Standard dosage 20 mg/kg orally every 8 hours per orum for 7 to 10 days. The maximum dose would be 1 g daily. Although not licensed by the United States Food and Drug Administration (FDA), the evidence supporting the use of acyclovir is Class I.

Contraindications Acyclovir is one of the safest medications licensed to date. There are no known contraindications to this medication.

Main drug interactions None reported.

Main side effects For oral therapy, nausea and vomiting occur at low frequency. Other notable side effects have not been reported.

Special points No studies have been done with valacyclovir or famciclovir in the treatment of this entity in children. Nevertheless, if an adolescent presented with clinical disease, most physicians would administer any of the three medications. For valacyclovir and famciclovir the evidence is Class III.

Cost/cost effectiveness No data available.

Genital herpes simplex virus therapy

- The aim of therapy is to decrease viral shedding, accelerate healing, and, for suppressive therapy, prevent recurrences.

Acyclovir

Standard dosage	For first episode disease, 200 mg orally five times or 400 mg orally three times daily for 7 to 10 days in the absence of complications. If complications develop, IV therapy is administered as for the immunocompromised host. For episodic therapy, 400 mg orally three times daily for 5 days. For suppressive therapy, 400 twice daily for 1 year. At 1 year, therapy should be discontinued to determine recurrence pattern. The evidence is Class I for studies done in adults and Class III for children.
Contraindications	Acyclovir is one of the safest medications licensed to date. There are no known contraindications to this medication.
Main drug interactions	None reported.
Main side effects	For oral therapy, nausea and vomiting occur at low frequency. Other notable side effects have not been reported.
Special points	No studies have been done with valacyclovir or famciclovir in the treatment of this entity in children. Nevertheless, if an adolescent presented with clinical disease, most physicians would administer any of the three medications. For valacyclovir and famciclovir the evidence is Class III.
Cost/cost effectiveness	First episode is $12.04; recurrent is $9.40. For chronic suppression, cost is $37.60.

Valaciclovir

Standard dosage	For first episode disease, 1 g twice daily for 7 to 10 days. For episodic therapy, 500 mg orally three times daily for 3 days. For suppressive therapy, 500 or 1000 mg orally daily. Treatment should be discontinued at 1 year to determine recurrence pattern. The evidence is Class I for adults and Class III for children.
Contraindications	None known.
Main drug interaction	None reported.
Main side effects	In addition to nausea and vomiting, a thrombotic thrombocytopenic purpura syndrome has been reported in patients with HIV infection at doses of 6 g daily.
Cost/cost effectiveness	First episode is $61.06; recurrent is $33.11. For chronic suppression, cost is $99.34.

Famciclovir

Standard dosage	For first episode disease, 250 mg orally three times daily for 5 to 10 days. For episodic therapy, 125 mg orally twice daily for 5 days. For suppressive therapy, 250 mg orally three times daily for 1 year and then discontinued as with acyclovir or valacyclovir.
Contraindications	None known.
Main drug interactions	None known.
Main side effects	The principle side effects are nausea and vomiting at very low frequency.
Cost/cost effectiveness	First episode is $52.55; recurrent is $30.75. For chronic suppression, cost is $210.20.

Herpes simplex keratoconjunctivitis therapy

Trifluorothymidine

Standard dosage	Two drops in the infected eye five times daily for 10 days.
Contraindications	None reported.
Main drug interactions	None reported.
Main side effects	Medication applied to the eye can lead to erythema of the conjunctivae and sclerea and punctuate lesions of the cornea.
Cost/cost effectiveness	The cost for trifluorothymide is $74.44.

Miscellaneous herpes simplex virus infections therapies—herpetic whitlow, herpes gladitorum, erythema multiforme

- The goal of therapy is to accelerate healing. Acyclovir is the treatment of choice as described previously for the immunocompromised host. Neither valaciclovir nor famciclovir have been studied under these circumstances. All evidence is Class III.

Pediatric considerations

- The judicious use of antiviral therapy in children requires appropriate application of both clinical skills and diagnostic aids. For life-threatening HSV infections of the brain, the deployment of polymerase chain reaction (PCR) for the detection of HSV DNA in cerebrospinal fluid is of the utmost of importance. It is essential for the clinician to identify a reliable laboratory that can expeditiously perform PCR assays with a high degree of reproducibility.

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