Published in final edited form as:
Clin Pharmacol Ther. 2010 November ; 88(5): 720–724. doi:10.1038/clpt.2010.192.

Treatment of Herpes Simplex Virus Infections in Pediatric Patients: Current Status and Future Needs

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Abstract

Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are members of the *Herpesviridae* family and are characterized by their ability to establish latency after primary infection and subsequently reactivate. HSV infections in the neonatal and pediatric populations range from uncomplicated mucocutaneous diseases to severe, life-threatening infections involving the central nervous system (CNS). The antiviral agent acyclovir has significantly improved treatment outcomes of HSV infections, including the frequency of mucocutaneous recurrences and mortality associated with CNS and disseminated infections.

CLINICAL PRESENTATIONS IN PEDIATRIC PATIENTS

In the United States, pediatric HSV infections are common; as many as 36% of children <14 years of age have serologic evidence of HSV-1 infection.[1] HSV causes lifelong infection, though the spectrum of diseases caused by HSV ranges widely depending on host factors such as age, immunocompetence, virus type, and the site of infection.[2] The following is an overview of the major clinical manifestations of HSV infections in the pediatric population.

Primary and recurrent mucocutaneous infections

Primary, or first-episode, HSV infection is usually asymptomatic. With symptomatic disease, orolabial, cutaneous, or anogenital infections are common. Extensive oral involvement, or gingivostomatitis, is more often seen in younger children, whereas pharyngitis is more typical of primary oral infections in older children and adolescents. First-episode anogenital HSV infections can occur in seropositive individuals (i.e., nonprimary infection), a scenario most commonly caused by HSV-2 infection in a person with preexisting HSV-1 antibodies. Primary anogenital infections are more likely to be associated with constitutional symptoms than are primary orolabial or cutaneous infections.

In immunocompetent hosts, primary infections are typically self-limiting and resolve in 10–21 days, during which time viral latency is established in the sensory ganglia corresponding to the area innervating the site of infection. Within the ganglia, reactivation of HSV leads to replication and subsequent neuronal transport, resulting in recurrence of mucocutaneous lesions or, more commonly, asymptomatic viral shedding. Immunocompromised hosts, especially those with impaired cell-mediated immune responses, are at greater risk for severe infections, including cutaneous dissemination and involvement of visceral organs, as

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

well as more frequent episodes of reactivation and prolonged durations of both clinical symptoms and viral shedding.[3]

Ocular infections

Primary or first-episode ocular infections are usually caused by HSV-1 and most commonly present as a blepharoconjunctivitis characterized by follicular conjunctivitis and the presence of vesicles at the margin of the eyelid. Severe cases can involve chemosis, pain, photophobia, or periorbital skin lesions and can progress to corneal ulcerations, although primary HSV blepharoconjunctivitis is more commonly self-limiting and nonscarring. As compared with adults, children have a higher incidence of bilateral ocular HSV infection and are more likely to have severe disease leading to corneal scarring and vision loss.[4] Latency is established in the trigeminal ganglia, where periodic viral reactivation leads to reinfection of affected ocular tissues (including the cornea, even if it was not affected during the initial disease process). Keratitis due to recurrent HSV infection is categorized as epithelial or stromal. Epithelial keratitis can be either scarring or nonscarring and involves active infection confined to the corneal surface, as seen in characteristic dendritic corneal ulcerations. Stromal keratitis, on the other hand, poses a greater threat to vision because it is an immune-mediated inflammatory response in the underlying corneal endothelial cells that leads to corneal scarring, thinning, and neovascularization.[5]

Neonatal infections

Seventy-five percent of neonatal HSV infections are due to HSV-2. The risk of transmission from a pregnant woman to the fetus is greatly increased in the context of first-episode primary maternal HSV during the third trimester of gestation, especially if there is prolonged rupture of membranes, vaginal delivery, or use of a fetal scalp electrode.[6] Peripartum transmission accounts for the majority of neonatal HSV infections (85%), and postpartum and *in utero* transmissions account for ~10 and ~5% of cases, respectively. The extent of disease in neonates with peripartum or postpartum acquired HSV infection is categorized as skin, eye, or mouth (SEM) disease, CNS disease, or disseminated disease. CNS disease accounts for 33% of neonatal HSV infections and may include the presence of SEM lesions but does not involve any other organ systems. Disseminated disease is associated with multiorgan involvement and makes up ~25% of the affected neonates; however, it is noteworthy that nearly two-thirds of disseminated cases also show CNS involvement.[7]

In the absence of antiviral therapy, disseminated disease is associated with a 1-year mortality rate of nearly 85%. Although untreated CNS disease carries a lower 1-year mortality rate (50%), in one study it was associated with long-term neurodevelopmental sequelae in 67% of survivors.[8] Antiviral therapy has improved outcomes, but even in the presence of appropriate therapy, CNS and disseminated neonatal HSV infections are both still associated with substantial morbidity and mortality.[9]

HSE

Beyond the first 3 months of life, HSV infection of the CNS occurs most significantly in the form of herpes simplex encephalitis (HSE), which is the most common cause of sporadic encephalitis in the United States.[10] Nearly all cases of HSE are due to HSV-1. One-third of HSE cases occur in the context of primary HSV infection, whereas ~67% occur as a result of either reactivation of latent HSV infection or acquisition of a new HSV strain in a previously infected person.[11,12] One-third of all HSE cases occur in patients <20 years of age, and typical clinical presentations include fever, altered mental status, and focal neurologic symptoms.[6] Hemorrhagic necrosis is a characteristic of the disease and is most typically

localized to the temporal lobe. The mortality rate of untreated HSE exceeds 70%, with impaired neurologic outcomes in almost all survivors. As with neonatal HSV infections, the advent of effective antiviral therapy has significantly improved patient outcomes, but morbidity and mortality remain unacceptably high.

CURRENT TREATMENT OF PEDIATRIC HSV INFECTIONS

Antiviral therapy

Early antiviral agents such as idoxuridine and vidarabine were evaluated for the systemic treatment of life-threatening HSV infections and proved to be of limited tolerability and efficacy.[8,13,14] With the development of acyclovir and other related acyclic nucleoside analogs such as valacyclovir and famciclovir, the management of HSV infections became more efficacious and also less toxic. Doses and duration of antiviral therapy for the treatment of HSV infections in pediatric patients are summarized in Table 1.

Acyclovir is a deoxyguanosine analog that must undergo a series of three phosphorylation steps before it can exert its antiviral effect of competitive inhibition on the viral DNA polymerase and termination of DNA chain elongation. Within an infected cell, the first phosphorylation of acyclovir occurs through the virally encoded thymidine kinase (TK), and the second and third phosphorylation steps are carried out by cellular kinases. Valacyclovir is the L-valyl ester oral prodrug of acyclovir and offers improved bioavailability. Famciclovir is the diacetyl ester prodrug of penciclovir, an acyclic guanosine analog. Much like acyclovir, penciclovir acts through a TK-dependent phosphorylation pathway, resulting in the active form of the agent, penciclovir triphosphate; the latter then acts as a competitive inhibitor of DNA polymerase. Unlike acyclovir, penciclovir is not incorporated into the lengthening DNA chain, and therefore it has no activity with regard to termination of DNA chain elongation.

Given that acyclovir, valacyclovir, and famciclovir are the mainstays of HSV treatment, the emergence of acyclovir-resistant HSV strains is a concern. In immunocompetent individuals infected with HSV, resistance to acyclovir has not yet become a clinically significant problem—the reported rates of resistance are <1%.[15] Resistance rates in immunocompromised patients, however, are slightly higher on average (5–6%), which should be kept in mind when managing these patients.[16] Mutations resulting in alterations or deficiency of TK are the most common mechanism of acyclovir resistance in HSV, although alterations of the viral DNA polymerase can result in resistance as well. Foscarnet, a pyrophosphate analog that directly inhibits viral DNA polymerase without the need for prior phosphorylation, and cidofovir, a nucleotide analog that inhibits DNA polymerase after a TK-independent phosphorylation process, are the two most common antiviral alternatives used to treat acyclovir-resistant HSV infections.

Idoxuridine and vidarabine are still available as topical preparations for the treatment of ocular herpes, as are other antiviral agents such as trifluorothymidine and acyclovir. In ocular infections, it is important to distinguish between epithelial keratitis and stromal keratitis; epithelial keratitis is treated with topical antiviral agents alone, whereas the immune-mediated stromal disease requires topical steroids and possibly systemic antiviral therapy as well. Topical penciclovir and acyclovir have been shown to have a modest effect in the context of recurrent orolabial infections in adults.[17]

For primary mucocutaneous HSV infections, including orolabial and anogenital disease, oral acyclovir, valacyclovir, and famciclovir have all been shown to hasten the resolution of symptoms as well as reduce the duration of viral shedding.[18,19] Therapy should be initiated early (within 72 h after the onset of symptoms) to achieve optimal benefit. Initiating oral

therapy at the first sign of recurrent mucocutaneous disease may alleviate symptoms somewhat, but the benefit is less substantial than is seen in primary HSV infections. Therefore, chronic suppressive therapy should be considered in patients with frequent mucocutaneous recurrences.

Suppressive therapy

In the context of recurrent mucocutaneous HSV infections, the decision to treat individual outbreaks (episodic therapy) or to use suppressive therapy (Table 2) is based primarily on the frequency of recurrences and the resultant debility of each patient. When taken chronically, oral acyclovir, valacyclovir, and famciclovir have all been shown to reduce the frequency of recurrence, the severity of individual episodes, and the degree of viral shedding in adults with recurrent mucocutaneous infections.[20] Because of their bioavailability and tolerability, valacyclovir and famciclovir are especially attractive options for chronic suppressive therapy in individuals with frequent recurrences, but these agents are considerably more expensive than acyclovir, and famciclovir is not currently available as a pediatric formulation.

Suppressive therapy following a completed course of intravenous acyclovir in patients with neonatal HSV infection may have a benefit as well. Some experts have recommended initiating suppressive therapy with oral acyclovir for neonates with HSV infection after the first mucocutaneous recurrence.[21] A previous phase I/II study evaluating oral acyclovir suppressive therapy in neonatal patients with HSV and SEM disease demonstrated a reduction in cutaneous recurrences, but nearly half of the infants receiving acyclovir developed neutropenia.[22] Two recent randomized controlled trials evaluating oral suppressive therapy in both SEM and CNS patients have been completed and are in the final stages of data analyses. The results are anticipated in the near future.

FUTURE NEEDS

Although acyclovir and the other guanosine derivative nucleoside analogs that are currently licensed to treat HSV infections have significantly improved our capacity to manage these conditions, novel therapeutic approaches are needed to improve I patient outcomes further. Prevention of HSV infection is the primary goal, whether by simply reducing transmission rates or, ideally, by developing a vaccine.[23] In the meantime, however, the importance of developing safe and effective antiviral agents must be emphasized.

When treating HSV infections of the CNS, a major limitation is the inability of nonlipophilic agents to penetrate adequately into infected brain tissue. Highly lipophilic antiviral agents have the ability to exert their antiviral activity in the affected CNS tissue more rapidly and achieve higher intracellular concentrations at the site of infection. The lipid ester analogs of cidofovir—hexadecyloxypropyl-CDV (CMX001) and octadecyloxyethyl-CDV—are more active *in vitro* than their parent agent against HSV-1 and HSV-2 and appear to penetrate into tissues more effectively as well.[24,25]

Several other novel HSV therapies are in various stages of evaluation. The helicase-primase complex inhibitors are a promising new class of antiviral agents with potent *in vitro* activity against HSV. BAY 57-1293 has been shown to have excellent activity specifically against HSV, and another recently reported helicase-primase inhibitor, ASP2151, demonstrated greater potency than acyclovir against HSV and varicella zoster virus.[26,27] N-methanocarbathymidine is a novel thymidine analog with potential utility against HSV as well as against orthopoxviruses.[28,29] Currently, there are no published data from clinical trials of these novel anti-HSV agents.

CONCLUSION

HSV infection is a common occurrence in the pediatric population. Although the incidence of life-threatening HSV disease is lower, HSV infection is still associated with substantial morbidity and mortality. Acyclovir and related compounds have significantly improved the efficacy and tolerability of treatment and suppression of HSV infections. Future directions include the continued development of safe and effective antiviral agents, as well as the development of vaccine candidates for further study.

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Table 1

Treatment of pediatric HSV infections

Orolabial	First episode	Acyclovir 75 mg/kg/day p.o. ÷ 5 times/day (max 1 g/day) × 7 days, or 5 mg/kg/dose i.v. 3 times/day × 5–7 days
		Valacyclovir[a] 1 g p.o. b.i.d. × 7 days, or 2 g p.o. b.i.d. × 1 day (if ≥12 y.o.)
		Famciclovir[a] 500 mg p.o. b.i.d. × 7 days (≥18 y.o.)
	Recurrent	Acyclovir 400 mg p.o. 5 times/day × 5 days
		Valacyclovir[a] 2 g p.o. b.i.d. × 1 day (≥12 y.o.)
		Famciclovir[a] 1.5 g p.o. ×1 day (≥18 y.o.)
Anogenital	First episode	Acyclovir 40–80 mg/kg/day p.o. ÷ 3–4 times/day × 5–10 days (max 1 g/day), or 1–1.2 g/day p.o. ÷ 3–5 times/day (if ≥12 y.o.) × 5–10 days, or 5 mg/kg/dose i.v. 3 times/day × 5–7 days
		Valacyclovir[a] 1 g p.o. b.i.d. 7–10 days (≥18 y.o.)
		Famciclovir[a] 250 mg p.o. t.i.d. × 7–10 days (≥18 y.o.)[30]
	Recurrent	Acyclovir 200 mg p.o. 5 times/day × 5 days (≥12 y.o.), or 400 mg p.o. t.i.d. × 5 days
		Valacyclovir[a] 500 mg p.o. b.i.d. × 3–5 days; 1 g p.o. daily × 5 days; 1 g p.o. b.i.d. × 1 day (≥18 y.o.)
		Famciclovir[a] 125 mg p.o. b.i.d. × 5 days, 500 mg p.o. b.i.d. × 5 days, or 1 g p.o. b.i.d. × 1 day (≥18 y.o.)
Neonatal	SEM	Acyclovir 60 mg/kg/day i.v. ÷ 3 times/day × 14 days
	CNS	Acyclovir 60 mg/kg/day i.v. ÷ 3 times/day × 21 days
	Disseminated	Acyclovir 60 mg/kg/day i.v. ÷ 3 times/day × 21 days
HSE	≤12 y.o.	Acyclovir 45–60 mg/kg/day i.v. ÷ 3 times/day × 14–21 days
	>12 y.o.	Acyclovir 30 mg/kg/day i.v. ÷ 3 times/day × 14–21 days
Ocular	Epithelial	Topical trifluorothymidine, vidarabine, idoxuridine, or acyclovir; no topical steroids
	Stromal	Topical trifluorothymidine, vidarabine, idoxuridine, or acyclovir; topical steroids indicated, also consider systemic acyclovir
Immunocompromised patients (localized, visceral, or disseminated)	<12 y.o.	Acyclovir 30 mg/kg/day i.v. ÷ 3 times/day × 7–14 days[30]
	≥12 y.o.	Acyclovir 15 mg/kg/day i.v. ÷ 3 times/day × 7–14 days[30]
	≥2 y.o.	Acyclovir 1 g/day p.o. ÷ 3–5 times/day × 7–14 days[30]
	Foscarnet[a]	80–120 mg/kg/day ÷ 2–3 times/day[30]
	Cidofovir[a]	Induction: 5 mg/kg/dose i.v. once weekly × 2 weeks[30] Maintenance: 5 mg/kg/dose i.v. once every 2 weeks[30]

b.i.d., twice daily; CNS, central nervous system; HSE, herpes simplex encephalitis; HSV, herpes simplex virus; i.v., intravenous; p.o., oral; SEM, skin, eye, or mouth; t.i.d., three times daily; y.o., years old.

[a]Insufficient data to determine pediatric dosing.

Table 2

Suppression of pediatric HSV infections

Orolabial	Acyclovir 40–80 mg/kg/day p.o. ÷ 3 times/day or 400 mg p.o. b.i.d./t.i.d. for adolescents; continue for up to 12 months, then reevaluate need
	Valacyclovir[a] 500 mg p.o. daily or 1 g p.o. once daily (≥18 y.o.)
	Famciclovir[a] 250 mg p.o. b.i.d. (≥18 y.o.)
Anogenital	Acyclovir 40–80 mg/kg/day p.o. ÷ 3 times/day or 400 mg p.o. b.i.d./t.i.d. for adolescents; continue for up to 12 months, then reevaluate need
	Valacyclovir[a] 500 mg p.o. daily or 1 g p.o. once daily (≥18 y.o.)
	Famciclovir[a] 250 mg p.o. b.i.d. (≥18 y.o.)
Following neonatal infection	Acyclovir 80 mg/kg/day p.o. ÷ 4 times/day 7 days for first recurrence; then 300 mg/m^2/dose p.o. t.i.d. × 6 months, then reevaluate need. Monitor CBC while on suppressive therapy[22]

b.i.d., twice daily; HSV, herpes simplex virus; p.o., oral; t.i.d., three times daily; y.o., years old.

[a] Insufficient data to determine pediatric dosing