Indian Academy of Pediatrics (IAP)

STANDARD TREATMENT GUIDELINES 2022

Herpes Simplex

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Herpes Simplex

Introduction

- ☑ Caused by two closely related viruses herpes simplex virus (HSV) Type 1 and HSV Type 2.
- ☑ Spectrum of infections depending on anatomic site, immune status of host and whether primary or recurrent infection.
- ☑ Infections mild and self-limiting except in immunocompromised, neonates and those with central nervous system (CNS) infection.
- ☑ *Primary infection* occurs in individuals not previously infected with HSV-1 or 2.
- ☑ *Nonprimary infection* in individuals already infected with one type, getting infected for the first time with the second type.
- ☑ *Latent infection* follows primary infection in regional sensory ganglion neurons where the virus is maintained in latent state for the rest of life of the host but periodically reactivates and causes *recurrent infections*.

Pathogenesis

- ☑ *Portal of infection:* Conjunctiva, mucosal epithelium of nose and mouth, abrasions due to scalp electrode or forceps delivery.
- ☑ Person to person close contact → transmission of infected secretions → viral replication in skin and mucous membrane → viremia → spread and replication in neural tissue → virus moves through neural arc characteristic herpetic lesions of skin and mucous membrane.
- ☑ Viremia can cause serious illness involving multi-organs in neonates, immunocompromised, and children with eczema and severe malnutrition.
- ☑ In neonates, source of infection is usually the mother.
- ☑ Virus may extend from nose to respiratory tract to cause pneumonia, via intraneuronal transport to cause encephalitis or spread hematogenously to viscera and the central nervous system.

Clinical Features

- ☑ Hallmarks of HSV are skin vesicles and shallow ulcers.
- ☑ Small 2–4 mm sized vesicles surrounded by erythematous base which evolve into shallow minimally erythematous ulcers after a few days.
- ☑ Most infections are asymptomatic.

Acute Oropharyngeal Infections (Herpetic Gingivostomatitis and Pharyngitis)

- ☑ Most commonly seen between 6 months to 5 years.
- ☑ Most frequent clinical manifestations of primary HSV-1 infection.
- ☑ Acute onset of extremely painful lesions, drooling, foul breath, refusal to feed and fever of up to 105°F.
- ☑ Swollen gums with vesicles throughout the oral cavity.
- ☑ Tonsillar exudates suggesting bacterial pharyngitis.
- ☑ Vesicles progress to form shallow indurated ulcers covered with yellow gray membranes.
- ☑ Untreated, the disease resolves in 7–14 days.

Herpes Labialis

- ☑ Most common manifestation of recurrent HSV 1 infection.
- ☑ Small grouping of erythematous papules over the lips and perioral area which progress to create small thin-walled vesicles. Complete healing occurs without scarring.

Herpetic Whitlow

- ☑ Herpetic infection of the fingers
- ☑ Most commonly seen in thumb sucking infants and toddlers with symptomatic or subclinical oral HSV 1 infection.

Genital Herpes

- ☑ In sexually experienced adolescents and young adults
- ☑ Infection from genital-genital (HSV 2) or oro-genital route (HSV 1)
- ☑ Periodic shedding of viruses from anogenital sites by symptomatic and asymptomatic individuals leading to infection in partners
- ☑ Short period of local burning and tenderness followed by vesicles which rupture to produce shallow tender ulcers with yellowish gray exudates
- ☑ Clinical recurrences common.

Clinical Features

Central Nervous System Herpes

- ☑ HSV (mainly HSV-1) causes sporadic encephalitis in children.
- ☑ Characterized by fever, headache, nuchal rigidity, nausea, vomiting, various neurologic signs and altered sensorium.
- ☑ Acute necrotizing infection involving frontal and/or temporal cortex and the limbic system.

Infections in Immuno-compromised Persons

- ☑ Severe life-threatening HSV infections in children with compromised immune functions such as in HIV or transplant recipients.
- ☑ Mucocutaneous infections—most common initial presentation.

Perinatal Infections

- ☑ HSV infection may be acquired in utero, during birth process or neonatal period.
- ☑ The risk of infection is greater in infants born to mothers with primary infection (30%) than with recurrent genital infections (2%).
- ☑ Neonates present with three patterns of disease:
  - Localized to skin, eyes or mouth (SEM) (40%)—presents at 5–11 days of life with a few vesicles at the presenting part or the site of trauma.
  - Encephalitis with or without SEM disease (30%)—presents at 8–17 days of life with clinical findings similar to bacterial meningitis. Skin vesicles only in 60% of cases. If untreated, 50% die.
  - Disseminated infection (30%)—involving multiple organs, including the brain, lungs, liver, heart, adrenals and skin; presents at 5–11 days of life with clinical picture similar to bacterial sepsis. May also exhibit respiratory distress, cyanosis, apneic spells, jaundice, purpuric rash and seizures. Skin vesicles seen in 75%. If untreated, 90% of these children die.

Diagnosis

- ☑ Usually made by history and clinical appearance of the lesions.
- ☑ If the pattern of the lesions is not specific to HSV, definitive diagnosis can be made by viral culture, or polymerase chain reaction (PCR) of the specimen from mucocutaneous lesions for HSV DNA.
- ☑ Direct fluorescent antibody testing, or Tzanck smear less sensitive and specific.
- ☑ Herpes simplex encephalitis (HSE) diagnosed by detecting HSV DNA from CSF PCR test. EEG changes and MRI findings form supporting evidence.
- ☑ In neonates, evaluation should include cultures of suspicious lesions as well as eye and mouth swabs and PCR of CSF and blood. In neonates, presence of elevated liver enzymes may provide indirect evidence of dissemination.

Treatment

- ☑ Three antiviral drugs commonly used are, acyclovir, valacyclovir and famciclovir.
- ☑ Intravenous acyclovir is the antiviral agent of choice for all categories of neonatal HSV infection, HSE and HSV infection in immunocompromised patients.

TABLE 1: Treatment of pediatric HSV infections.

Orolabial	First episode	Acyclovir 75 mg/kg/day po ÷ 5 times/day (max 1 g/day) × 7 days, or 5 mg/kg/dose IV 3 times/day × 5–7 days
		Valacyclovir* 1 g pobid × 7 days, or 2 g pobid × 1 day [if ≥12 years of age (*yo*)]
	Recurrent	Acyclovir 400 mg po 5 times/day × 5 days
		Valacyclovir* 2 g pobid × 1 day (≥12 *yo*)
Anogenital	First episode	Acyclovir 40–80 mg/kg/day po ÷ 3–4 times/day × 5–10 days (max 1 g/day), or 1–1.2 g/day po ÷ 3–5 times/day (if ≥12 *yo*) × 5–10 days, or 5 mg/kg/dose IV 3 times/day × 5–7 days
	Recurrent	Acyclovir 200 mg po 5 times/day × 5 days (≥12 *yo*), or 400 mg potid × 5 days
		Valacyclovir* 500 mg pobid × 3-5 days; 1 g po daily × 5 days
		Famciclovir* 125 mg pobid × 5 days, 500 mg pobid × 5 days
Neonatal	SEM	Acyclovir 60 mg/kg/day IV ÷ 3 times/day × 14 days
	CNS	Acyclovir 60 mg/kg/day IV ÷ 3 times/day × 21 days
	Disseminated	Acyclovir 60 mg/kg/day IV ÷ 3 times/day × 21 days
HSE	≤12 yo	Acyclovir 45-60 mg/kg/day IV ÷ 3 times/day × 14-21 days
	>12 yo	Acyclovir 30 mg/kg/day IV ÷ 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 yo	Acyclovir 30 mg/kg/day IV ÷ 3 times/day × 7–14 days
	≥12 yo	Acyclovir 15 mg/kg/day IV ÷ 3 times/day × 7–14 days
	≥2 yo	Acyclovir 1 g/day po ÷ 3-5 times/day × 7–14 days
	Foscarnet*	80–120 mg/kg/day ÷ 2–3 times/day
	Cidofovir*	*Induction:* 5 mg/kg/dose IV once weekly × 2 weeks *Maintenance:* 5 mg/kg/dose IV once every 2 weeks

*Insufficient data to determine pediatric dosing.

Further Reading

- ☑ Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children. [Online] Available from: https://clinicalinfo.hiv.gov/en/guidelines/pediatric-opportunistic-infection/whats-new. downloaded 18 February 2022
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