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Herpes Simplex

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Drs Chayavichitsilp,
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Objectives After completing this article, readers should be able to:

1. Characterize the epidemiology of herpes simplex virus (HSV) infection, including mode of transmission, incubation period, and period of communicability.
2. Recognize the difference in clinical manifestations of HSV1 and HSV2 infection.
3. Diagnose various manifestations of HSV infection.
4. Describe the difference in the clinical manifestations and outcome of HSV infection in newborns and older infants and children.
5. Discuss the management of HSV infection.
6. List the indications and limitations of oral acyclovir treatment for HSV infection.

Introduction

HSV causes a contagious infection that affects approximately 60% to 95% of adults worldwide. HSV1 and HSV2 primarily infect human populations. HSV1 is associated chiefly with infections of the mouth, pharynx, face, eye, and central nervous system (CNS), and HSV2 is associated primarily with infections of the anogenital region, although both serotypes may infect any area. (1)

Epidemiology

Most adults are infected with HSV and carry latent viruses, but the serotype, severity of symptoms, and mode of transmission vary with age. Children are infected primarily with orolabial HSV1 by 5 years of age, with infection rates of 33% in populations that are of lower socioeconomic status and 20% in those who have improved socioeconomic status. By adulthood, HSV1 affects 70% to 80% in the lower socioeconomic population and 40% to 60% in the higher socioeconomic population. (1) Globally, the prevalence of HSV1 increases consistently with age, reaching 40% by age 15 years and increasing to 60% to 90% in older adults. (2) In the United States, the prevalence of HSV1 increases consistently with age, from 26.3% in 6- to 7-year-old children and 36.1% in 12- to 13-year-old children to 90% among those older than 70 years. (2)(3) Of note, the overall prevalence of HSV1 in the United States has been shown to be decreasing over time. (3)

Worldwide, the prevalence of HSV1 infection is greater than HSV2 infection in most geographic areas. HSV2 primarily is sexually transmitted and, therefore, is not as common in young children. However, HSV2 can be transmitted from mother to neonate during pregnancy, with a neonatal incidence between 1 in 3,000 and 1 in 20,000 live births and approximately 1,500 new cases in the United States annually. Approximately 2% of women acquire genital herpes during pregnancy, and about 20% to 30% of pregnant women are seropositive for HSV2. (4) The prevalence of HSV2 varies across country, sex, and age. HSV2 prevalence is highest in areas of sub-Saharan Africa and parts of Central and South America. The prevalence usually is lower in western and

Abbreviations

CNS:	central nervous system
CSF:	cerebrospinal fluid
DFA:	direct fluorescent antibody
HAEM:	HSV-associated erythema multiforme
HHV:	human herpesvirus
HSV:	herpes simplex virus
IV:	intravenous
PCR:	polymerase chain reaction
SEM:	skin, eye, and mouth
STI:	sexually transmitted infection
VZV:	varicella-zoster virus

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southern Europe than in northern Europe and North America. The lowest rates of HSV2 prevalence are found in Asia.

Generally, the prevalence is higher in women than in men and increases with age from negligible levels in children younger than 12 years to 20% to 40% by the age of 40 years and as high as 80% among higher-risk populations. (1)(2)(5)(6) In the United States, the prevalence of HSV2 infection in African Americans is much higher than in whites or Mexican Americans. Although time trends in HSV prevalence are limited, most studies suggest that the prevalence of HSV2 has increased over the past few decades in countries such as the United States from 16.0% in the late 1970s to 20.8% in the early 1990s; in other populations, HSV2 prevalence has either remained stable or decreased. (2)

As stated previously, HSV2 is associated primarily with infections of the anogenital region, whereas HSV1 is found extragenitally. Recent studies, however, have shown a 30% increase in the prevalence of HSV2 infection, (7) with HSV2 being as common as HSV1 in the extragenital regions except for the orofacial area. Furthermore, HSV1 appears to be increasing in prevalence in the anogenital region, previously known to be infected predominantly by HSV2.

Etiology

There are more than 80 herpesviruses, eight of which are capable of infecting humans. In addition to HSV1 and HSV2, varicella-zoster virus (VZV), cytomegalovirus, Epstein-Barr virus, human herpesviruses (HHV6 and HHV7), and Kaposi sarcoma-associated herpesvirus (HHV8) can infect humans. All herpesviruses are enveloped, double-stranded DNA viruses that have highly organized genomes encoding more than 84 polypeptides. (6) Although the DNA sequences of HSV1 and HSV2 are very similar, the proteins within the envelope allow serologic distinction between the two.

Transmission

Infection is transmitted primarily through exposure to mucous membranes or skin that have active lesions or to mucosal secretions of an individual who has an active HSV infection. The virus is transmitted most easily through saliva and can remain stable outside of the host for short periods of time, allowing transmission for some time after direct mucocutaneous contact with the virus. HSV also can be transmitted through respiratory droplets or by exposure to mucocutaneous secretions from an asymptomatic person who is shedding virus. Shedding

refers to the presence of viruses outside of the cells on the skin surface, despite the absence of clinical signs. (1)

The initial or primary HSV1 or HSV2 infection usually has an incubation period of approximately 4 days, but can range from 2 to 12 days. This is followed by an active viral shedding period that lasts at least 1 week and up to several weeks. Most patients who are primarily infected with HSV are asymptomatic. Therefore, the virus still can be actively transmitted during the period of incubation and viral shedding without the occurrence of active skin lesions. (1)

After initial infection, the virus usually remains latent, persisting within the sensory ganglia of the autonomic nervous system, and the infection can be considered incurable. Within the autonomic ganglia, the virus replicates while evading detection by the host immune system. (1)(6) HSV1 resides most commonly within the trigeminal ganglion, due to its primary target site in and around the oral areas; HSV2 primarily remains in sacral ganglia after infection of the genital region. Once triggered to reactivate by an internal or external stimulus, including stress, exposure to sunlight, fever, and menstruation, the virus can travel along the sensory nerve and reactivate in the same mucocutaneous region as the initial infection. Symptoms normally last for a shorter period of time than for the initial infection, and viral shedding only lasts 3 to 4 days. On average, reactivation of HSV occurs during approximately 1% of the days in the life of patients infected previously. (8)

Diagnosis

Several methods are employed to diagnose the presence of HSV infection, each having varying degrees of selectivity, sensitivity, cost, and utility. The main clinical method for diagnosing primary HSV1 infection is recognizing the classic presentation of herpetic lesions in or around the oral cavity. Monomorphous, grouped vesicles on an erythematous base evolve into coalescing, crusted papules and plaques within 1 to 3 days. The lesions have a propensity to erode or ulcerate. Initial infection can lead to an extensive gingivostomatitis. In contrast to HSV1, the initial diagnosis for HSV2 can be more difficult because the classic signs of genital herpes, herpetic ulcers in and around the genital area, may not be present. In neonates, the presence of vesicular lesions should raise high suspicion for HSV infection.

Laboratory evaluations can be used to confirm an initial diagnosis or further investigate a suspicion of HSV infection. The gold standard for laboratory diagnosis is the viral culture. The viral culture technique can be employed only with active lesions and is obtained best by

vigorously swabbing the base of an unroofed vesicle. The swab is inoculated into a prepared cell culture, and the inoculated cells are observed for characteristics of HSV infection, including multinucleated giant cells and desquamated epithelial cells with intranuclear inclusions. Such findings usually are observed within 2 to 7 days after inoculation and can confirm the presence of HSV infection. If the inoculated cell culture is devoid of characteristic signs of HSV infections for more than 15 days, the sample is reported as negative. Although this method offers a relatively rapid and effective method of diagnosing HSV infection, it can be limited by the quality of swabbing and culture techniques.

The Tzanck smear is a rapid and reasonably priced diagnostic test that can confirm the presence of HSV infection. Cells scraped from the base of a freshly opened vesicle are stained and evaluated for the characteristic cytopathology of HSV infected cells, including multinucleated giant cells and eosinophilic intranuclear inclusions (Fig. 1). Although the test can confirm the presence of HSV or VZV, it cannot differentiate between the two herpes serotypes and, therefore, cannot diagnose HSV1 or HSV2 infection definitively. In addition, the sensitivity and specificity of the test are highly variable, depending on the evaluator. An experienced clinician, such as an infectious disease specialist or pathologist, should interpret test results because the findings may be subtle. With the increasing availability of the direct fluorescent antibody (DFA) technique, the Tzanck smear has decreased in popularity as a diagnostic alternative.

DFA testing is an immunohistochemistry technique that uses a specific antibody to identify the presence of

viral antigens. The antibody is tagged with fluorescent agent and forms an antigen-antibody complex with HSV antigens present within a tissue or smear specimen. The process can be performed with cytologic preparations, such as the Tzanck smear, as well as virally inoculated cell cultures. In addition, DFA may be employed to serotype the HSV infection. Because DFA testing is rapid, sensitive, inexpensive, and virally selective, it often is used to substantiate clinical suspicion and determine serotype.

A punch, shave, or wedge tissue biopsy also may be used to detect the presence of HSV infection and is especially helpful when a suspicious lesion is old or atypical. The biopsied cells are observed microscopically to detect degenerative cytopathologic changes commonly associated with the infection. The degenerative changes present in cells infected with HSV1 and HSV2 also are observed in cells infected with VZV. Thus, the specificity of the technique is low, and the test cannot be used to serotype the infection.

Amplification of viral DNA using polymerase chain reaction (PCR) is another method for detecting the putative presence of viral DNA. This method is particularly useful for detecting the presence of HSV in the cerebrospinal fluid (CSF) of patients suspected of having herpes encephalitis. As HSV PCR becomes more readily available and less expensive, it has the potential to become the most widely used means of detecting HSV for all types of infection because it is rapid, highly reliable, and valid.

Serologic assays are employed to detect the presence of HSV antibodies when other techniques are impractical or ineffective. Such assays take longer to complete than other techniques and should be considered primarily for diagnosing recurrent infections, in the presence of healing lesions and the absence of active lesions, or when partners of persons who have clinical herpes are at risk. Sera are collected at two separate times; acute serum is obtained within 3 to 4 days after the onset of the initial symptoms and convalescent serum is gathered several weeks after the symptoms have abated. To confirm a diagnosis of primary HSV infection, the acute sample should be devoid of HSV-positive antibodies due to the delayed humoral response, and the convalescent sample should demonstrate the presence of both immunoglobulin G and M antibodies to HSV proteins. If any quantities of antibodies are observed in the acute sample, primary infection is ruled out and the diagnosis is recurrent herpes infection. The absence of antibodies in both samples indicates a negative test, which should be verified later by another serologic assay. In the absence of herpetic lesions, traditional serologic assays cannot deter-

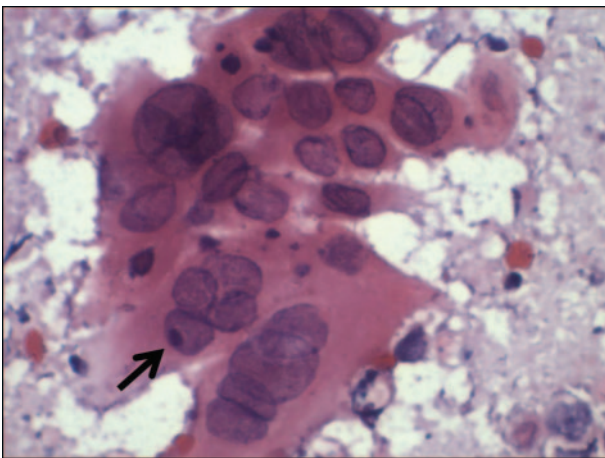


Figure 1. A positive Tzanck smear showing a multinucleated giant cell and intranuclear inclusions (arrow). Courtesy of Dr Robert O. Newbury.

mine the serotype or whether the site of infection is oral or genital. However, newer type-specific serologic assays can be performed to test for antibodies to both HSV1 and HSV2 proteins.

Several transport media are available for effective viral transport after collection of the specimen, including swabs, liquid media, and cell cultures. Studies suggest that although there are slight differences in the survivability of both HSV1 and HSV2 in different media, most media are effective as long as the temperature is tightly controlled, preferably at 39.2°F (4.0°C), and transport times are kept to a minimum, preferably less than 24 hours and no greater than 48 hours. (9) Survival of the virus at temperatures greater than 39.2°F (4.0°C) and transport times greater than 48 hours for all transport media is variable and more dependent on viral concentration and accurate laboratory techniques.

Clinical Manifestations

The clinical presentation of HSV infection is variable and dependent on method of transmission, age, and immunocompetency of the host. Cutaneous lesions usually consist of small, monomorphous vesicles on an erythematous base that rupture into painful, shallow, gray erosions or ulcerations with or without crusting. (10) The skin lesions typically are preceded by prodromal symptoms such as burning and paresthesia at the site, lymphadenopathy, fever, malaise, myalgia, loss of appetite, and headaches. Most initial infections are subclinical and may be unrecognized. Recurrent infections due to reactivation of the latent viruses in the dorsal root ganglia are more localized, milder, and shorter in duration. They tend to occur following triggers such as stress, menstruation, exposure to sunlight, and fatigue. Both primary and recurrent HSV infections can manifest on any mucocutaneous surface. Table 1 summarizes the clinical manifestations, differential diagnoses, and recommended treatments of herpetic infections occurring after the neonatal period.

Herpetic Gingivostomatitis

Herpetic gingivostomatitis presents as multiple round ulcers or superficial erosions commonly affecting the palate, tongue, and gingivae. It is caused much more commonly by HSV1. Patients may present with the typical prodromal symptoms, followed by classic vesiculoulcerative lesions. Children may present with diffuse erythema and swelling of the gingiva, drooling, foul-smelling breath, and anorexia. Such nonspecific signs and symptoms can be caused by a wide range of conditions, including Coxsackievirus infections, erythema multi-

forme, pemphigus vulgaris, acute necrotizing ulcerative gingivitis, and most commonly, aphthous stomatitis. Aphthous stomatitis can be differentiated from herpetic gingivostomatitis by the absence of a vesicular stage, prodrome, and systemic signs and symptoms. The major complication of herpetic gingivostomatitis is dehydration in children whose painful lesions result in poor fluid intake. Thus, pain control and sufficient rehydration comprise the mainstay of management.

Herpes Labialis

Herpes labialis is the most common manifestation of HSV1 infection. Because most initial infections are asymptomatic and may be unrecognized, recurrent orofacial herpes (commonly called fever blisters or cold sores) typically is the initial manifestation in children and young adults. The outer vermilion border is a common location, and the crusted lesions often are confused with staphylococcal or streptococcal impetigo (Figs. 2, 3). Secondary bacterial infections with *Staphylococcus* or *Streptococcus* also may occur and are characterized by honey-colored crusting on top of the classic herpetic lesions. Treatment with oral acyclovir can be effective if started within 1 to 2 days of prodromal symptoms. Chronic suppressive therapy with an oral antiviral medication can reduce the frequency of recurrences and is recommended for patients who experience six or more outbreaks per year. (8) Topical acyclovir is ineffective in immunocompetent hosts and, therefore, is not recommended.

Genital Herpes

Genital herpes (Fig. 4) most commonly is caused by HSV2, although the proportion due to HSV1 has been increasing recently. (1) This sexually transmitted infection (STI) is associated with risk factors such as lower socioeconomic status, sexual promiscuity, geography, race, and education. (1) Differential diagnoses include other STIs such as syphilis, chancroid, condyloma acuminata, and lymphogranuloma venereum, and non-STIs such as *Candida* infection, scabies, lichen planus, lichen sclerosis, Behçet syndrome, herpes zoster, and trauma. Sexual abuse must be suspected in prepubertal children who develop genital herpes. Complications include urinary retention, psychological morbidity, and aseptic meningitis. The pathogenesis of the spread to the CNS is unclear, but two routes are possible, including the hematogenous route and direct spread from mucocutaneous sites through the peripheral nerves. Treatment with oral antiviral medication can be effective if started early. For

Table 1. Clinical Manifestations, Differential Diagnoses, and Recommended Treatments of Herpes Simplex Virus Infections

Clinical Manifestation	Differential Diagnoses	Recommended Treatment
Herpetic Gingivostomatitis	<ul style="list-style-type: none"> • Herpangina • Hand-foot-and-mouth disease • Erythema multiforme • Pemphigus vulgaris • Acute necrotizing ulcerative gingivitis • Aphthous stomatitis 	<ul style="list-style-type: none"> • Pain control and rehydration • Insufficient data regarding response to antiviral treatment, but many experts treat severe cases
Herpes Labialis	<ul style="list-style-type: none"> • Impetigo 	<ul style="list-style-type: none"> • For primary disease and recurrences, oral acyclovir has limited therapeutic benefits in immunocompetent hosts, but many experts treat severe cases • Suppression for recurrent episodes*
Genital Herpes	<p><u>Sexually transmitted infections:</u></p> <ul style="list-style-type: none"> • Syphilis • Chancroid • Condyloma acuminatum • Lymphogranuloma venereum <p><u>Non-sexually transmitted infections:</u></p> <ul style="list-style-type: none"> • <i>Candida</i> infections • Scabies • Lichen planus • Lichen sclerosis • Behçet syndrome • Herpes zoster • Trauma 	<ul style="list-style-type: none"> • Primary: Oral acyclovir 1,000 to 1,200 mg/day for 7 to 10 days • Recurrences: Oral acyclovir 1,000 to 1,200 mg/day for 3 to 5 days • Suppression*
Herpetic Keratoconjunctivitis	<ul style="list-style-type: none"> • Scleritis • Iritis • Glaucoma • Conjunctivitis • Herpes zoster 	<ul style="list-style-type: none"> • Prompt referral to ophthalmology • Trifluridine 1%, iododeoxyuridine 0.1%, and vidarabine 3% ophthalmic ointments • Suppression*
Herpetic Whitlow	<ul style="list-style-type: none"> • Bacterial felon • Paronychia • Blistering dactylitis • Burn • Impetigo 	<ul style="list-style-type: none"> • Supportive • Antiviral therapy early in the course can be considered
Herpes Gladiatorum	<ul style="list-style-type: none"> • Atopic dermatitis • Contact dermatitis • Impetigo • Tinea corporis 	<ul style="list-style-type: none"> • Avoid contact sports until lesions have become dry and firm and crusts are adherent • Suppression throughout sports season is controversial
Herpes Encephalitis	<ul style="list-style-type: none"> • Other bacterial and viral encephalitis 	<ul style="list-style-type: none"> • Intravenous acyclovir for 21 days
Eczema Herpeticum	<ul style="list-style-type: none"> • Atopic dermatitis flares • Impetigo 	<ul style="list-style-type: none"> • Intravenous acyclovir usually recommended • Oral antibiotic therapy for secondary bacterial infection • Topical emollients • Topical steroids as needed • Avoid topical calcineurin inhibitors
<p>*If recurrences involve six or more episodes per year, oral acyclovir 80 mg/kg per day or 800 to 1,200 mg/day continuously up to 12 months is recommended. Data from <i>Red Book: 2006 Report of the Committee on Infectious Diseases</i>. (8)</p>		

patients experiencing frequent recurrences (at least six episodes per year), chronic suppressive therapy with an oral antiviral is recommended. (8)

Herpetic Keratoconjunctivitis

Ocular HSV infection is the second most common infectious cause of blindness worldwide. HSV1 is the predom-



Figure 2. An early vesicle on an erythematous base at the vermilion border in herpes labialis. Reprinted with permission from Dr Sheila F. Friedlander.

inant cause. Vesicles, followed by erosion or ulceration of the cornea, appear along with purulent conjunctivitis. Differential diagnoses include scleritis, iritis, glaucoma, conjunctivitis, and herpes zoster. Prompt referral to ophthalmology is recommended to prevent complications such as permanent scarring, secondary bacterial infection, meningoencephalitis, and vision loss. Neonates afflicted with ocular HSV may have associated systemic or CNS disease. Treatment consists of both topical ophthalmic antiviral (trifluridine, vidarabine, idoxuridine) and oral antiviral medications.

Herpetic Whitlow

Herpetic whitlow presents with deep-seated swelling, erythema, and vesiculoulcerative lesions on the pulp of



Figure 3. Vesicles and crusting on the vermilion border, typical location of herpes labialis. Reprinted with permission from Dr Victoria R. Barrio.



Figure 4. Multiple monomorphic vesicles on an erythematous base on the penile shaft and scrotum that are characteristic of genital herpes. Reprinted with permission from Dr Sheila F. Friedlander.

the distal phalanx of the hand (Fig. 5). This infection occurs commonly in patients who have primary oral or



Figure 5. Herpetic whitlow, showing deep-seated vesicles grouped in clusters on the digit. Reprinted with permission from Dr Sheila F. Friedlander.

genital herpes (due to autoinoculation) and health-care workers. In children, digital/oral contact is the most common cause of herpetic whitlow. In adolescents and adults, digital/genital contact is more common, making HSV2 the predominant infectious agent of herpetic whitlow. Differential diagnoses include bacterial felon or paronychia, blistering dactylitis, burn trauma, and impetigo. (10) Oral antiviral medications are optional and are used in extensive disease.

Herpes Gladiatorum

Herpes gladiatorum occurs in those involved in contact sports such as wrestling, boxing, football, soccer, and rugby. It most commonly affects exposed areas such as the face, ears, upper extremities, and neck. HSV1 is more likely to be the agent than HSV2, due to the nature of transmission. Differential diagnoses include atopic dermatitis, contact dermatitis, impetigo, and tinea corporis. Patients who have herpes gladiatorum should avoid contact sports during outbreaks until the culture results are negative. (11) Measures to prevent transmission also should be practiced and include examining athletes for active lesions and excluding them from competition and cleaning wrestling mats with bleach for at least 15 seconds of contact time between matches. (8) The National Collegiate Athletic Association recommends that athletes not be allowed to participate until the crusts are firm and adherent. (11) If the lesions have not crusted over or the crusts are not completely dry, the possibility is high that the patient still is infectious. Cultures to verify the noninfectious state should be performed after the crusts are dry, firm, and adherent. The family of an affected patient must be informed and instructed to perform appropriate preventive measures. Suppressive therapy is likely to be effective, but data about such therapy are insufficient, and the family needs to be made aware of this limitation before the initiation of therapy.

Herpes Encephalitis and Meningitis

HSV encephalitis can be a manifestation of primary or recurrent infections. Patients present with nonspecific CNS symptoms such as altered mental status, personality changes, seizures, and focal neurologic findings. HSV meningitis is characterized by CSF pleocytosis, with lymphocyte predominance and red blood cells in the CSF. HSV also is believed to cause a rare form of aseptic meningitis, termed Mollaret syndrome, consisting of recurrent episodes of severe headache, meningismus, and fever that resolve spontaneously.

Complications include Bell palsy, atypical pain syndromes, trigeminal neuralgia, ascending myelitis, and

postinfectious encephalomyelitis. Therapy is less effective in older adults than in children. Therefore, the recommended treatment for adults (parenteral acyclovir for 21 days) also is recommended for pediatric patients who have herpes infections of the CNS. (8)

Neonatal Herpes

Neonatal herpes occurs in 1 in every 3,000 to 20,000 live births and affects approximately 1,500 to 2,000 infants per year in the United States. (8) In addition, 40% to 50% of infants born to mothers afflicted with primary genital lesions are affected compared with only 2% to 3% of those born to women undergoing recurrences. (10) Up to 70% of infants who have neonatal herpes are born to asymptomatic mothers, adding to the difficulty in diagnosing this disease.

Neonatal herpes manifests in the first 4 weeks after birth and consists of three different types based on clinical manifestations: 1) skin, eye, and mouth (SEM), 2) CNS (often presenting with seizures, lethargy, and hypotonia), and 3) disseminated (including liver, adrenal glands, lungs). Classic cutaneous lesions generally are located on the scalp, mouth, nose, and eye, where the infant's skin comes into contact with the mother's genital lesions (Fig. 6). CNS infection presents with neurologic signs such as seizures and accounts for 60% of the cases. Skin lesions also are noted. Permanent neurologic disability can affect up to 40% of survivors. Disseminated neonatal HSV is a devastating manifestation that is associated with a mortality rate of at least 50%. Infants present with multisystem involvement (shock, disseminated intravascular coagulation, and multiple organ system failure).



Figure 6. Cluster of vesicles on the forehead and periocular area characteristic of neonatal herpes simplex. Reprinted with permission from Friedlander SF, Bradley JS. Viral infections. In: Eichenfield LF, Frieden IJ, Esterly NB, eds. *Neonatal Dermatology*. 3rd ed. Philadelphia, Pa: Saunders; 2008:193–197.

The differential diagnosis of neonatal HSV infection includes bacterial sepsis and viral infections such as enteroviruses, varicella, influenza A and B, parainfluenza, and adenovirus. Incontinentia pigmenti and Langerhans cell histiocytosis also may present with vesicles and must be differentiated from HSV by using the diagnostic techniques described previously.

HSV is transmitted most commonly during delivery, but also can be transmitted in utero or through postnatal contact with the mother or other caretakers. It is not transmitted through human milk. Higher risks of transmission are associated with younger age of the mother, maternal seronegativity, the presence of genital lesions during vaginal delivery, and infant prematurity.

Because of high rates of morbidity and mortality, timely diagnosis and prompt initiation of treatment are crucial. A high degree of suspicion is required in neonates who have vesicular skin lesions, sepsis syndrome with negative bacteriologic culture results, severe liver dysfunction, fever, irritability, and abnormal CSF findings, particularly if seizures are present. Because of the low toxicity profile of the antiviral medications and the potentially severe post-HSV sequelae, it always is better to institute therapy pending culture results if significant suspicion exists.

Prevention also is crucial, although there is no consensus on the optimal prevention strategy. Pregnant mothers who are seronegative and have seropositive sexual partners should be counseled to maintain abstinence near term. For those who acquire primary genital HSV during late pregnancy, the National Guideline Clearinghouse states, "Some specialists recommend acyclovir therapy, some recommend routine cesarean section and others recommend both." (12) However, for those who have a history of recurrent genital HSV, a Cochrane review found insufficient data to support the use of prophylactic acyclovir. (13)

Congenital HSV

Congenital HSV describes an HSV2 infection of the fetus that has occurred prenatally. Infected fetuses often die in utero. However, those that survive to term typically present with vesicular lesions, chorioretinitis, microphthalmia, microcephaly, and abnormalities on brain scan.

Congenital HSV in neonates can be differentiated from neonatal HSV by the absence of signs of systemic toxicity and overwhelming sepsis in the former as well as the presence of both fetal and maternal antibodies against HSV. Other differential diagnostic considerations include congenital varicella syndrome and syphilis.

Treatment is similar to that for neonatal HSV, although the neurologic prognosis is poor, and virtually all affected infants exhibit developmental delay.

Eczema Herpeticum

Eczema herpeticum also is known as Kaposi varicelliform eruption. It is characterized by HSV infections of skin from an underlying barrier defect caused by atopic dermatitis, pemphigus, Darier disease, burn trauma, and cosmetic procedures. (1) The lesions tend to coalesce into large, superficial erosions and often are disseminated (Figs. 7 and 8). Differential diagnoses include atopic dermatitis flares, impetigo, and secondarily infected lesions. Management includes intravenous (IV) antiviral therapy, antibiotic therapy for secondary bacterial infection, and topical emollients. (10) Most experts use anti-inflammatory therapy such as topical corticosteroids in areas of atopic dermatitis once systemic antiviral therapy has been initiated. However, the use of calcineurin inhibitors is contraindicated in eczema herpeticum. (14)

Herpes in the Immunocompromised Host

HSV infections in immunocompromised individuals such as those who have hematologic malignancy, immune deficiencies, acquired immunodeficiency syndrome, and organ transplants tend to have higher risks of dissemination and longer durations of outbreaks and are less responsive to therapy. (10) Complications include esophagitis, tracheobronchitis, pneumonitis, hepatitis, pancreatitis, and adrenal necrosis. The skin lesions often



Figure 7. Eczema herpeticum, limited, showing vesicles and crusts coalescing into plaques on underlying eczematous skin in the popliteal fossa, a typical location affected by atopic dermatitis. Reprinted with permission from Dr Sheila F. Friedlander.



Figure 8. Eczema herpeticum, disseminated, showing rapidly progressing vesicles over an erythematous base that coalesced into plaques and then crusted over diffusely on the face of a young child who has underlying atopic dermatitis. Reprinted with permission of Dr Sheila F. Friedlander.

are atypical and can be extensively crusted, pustular, necrotic, or exophytic. The differential diagnosis involves herpes zoster and similar conditions, depending on the location of the outbreak. Prompt therapy with parenteral antiviral medications is critical.

HSV-associated Erythema Multiforme

HSV-associated erythema multiforme (HAEM) is a complication of HSV outbreaks that induces erythema multiforme skin lesions. Patients commonly present with fixed target or “bull’s eye” lesions distributed diffusely on the body, with a predilection for palms and soles. The lesions generally occur within 10 days of oral or genital HSV reactivation (Figs. 9 and 10). (1) This condition tends to resolve spontaneously without complications. However, patients experiencing frequent outbreaks may benefit from chronic suppressive antiviral prophylaxis.



Figure 9. Target lesions of different sizes on palm that are characteristic of erythema multiforme. Reprinted with permission of Drs Sheila F. Friedlander and Bari B. Cunningham.

Principles of Management

Management of HSV infections often incorporates both treatment and prevention of recurrences. Because of the infectious nature of the virus and the risk it poses to the neonate and immunocompromised individuals, prevention of recurrences is important and should be practiced in every patient.

Prevention

Prevention of transmission is the first step in the management of HSV infections. Patients should be educated regarding the nature of the disease, transmission through sexual and nonsexual contact, and asymptomatic shedding of the virus. Patients who have active lesions on the



Figure 10. Target lesions of different sizes on soles characteristic of erythema multiforme. Reprinted with permission of Drs. Sheila F. Friedlander and Bari B. Cunningham.

skin should avoid direct contact with others. Precautions include: 1) the use of condoms or other barrier methods during sexual intercourse for genital HSV; 2) the avoidance of contact sports, examination and exclusion of athletes who have active lesions, and cleaning of wrestling mats with bleach after every match for herpes gladiatorum; and 3) the use of condoms or abstinence for pregnant women who are seronegative whose partners are seropositive to prevent primary HSV infections during the third trimester of the pregnancy. The multiple risk factors that precipitate recurrence (eg, stress, exposure to sunlight, fever, menstruation, and trauma to the area such as dental procedures) should be addressed with patients.

In a hospital, contact precautions should be practiced by all health-care personnel for all patients possibly infected with HSV except for those whose infections are limited to encephalitis and meningitis. These measures include providing the patient with a single-patient room when possible; using gloves at all times; washing hands after glove removal; and wearing gowns during direct contact with a patient, environmental surfaces, or items in the patient's room.

Treatment

The treatment of HSV infections does not result in cure, but can attenuate the duration of the clinical course, decrease severity, prevent complications, and reduce the frequency of recurrence. Current treatments include supportive therapy and oral, parenteral, and topical antiviral medications.

SUPPORTIVE THERAPY. Supportive therapy encompasses pain control and rehydration. Such support is particularly important for children afflicted with herpes labialis and gingivostomatitis. Because of pain, patients may refuse to eat or drink, resulting in dehydration. Pain control with local anesthetics and oral or IV rehydration may be useful.

ORAL ANTIVIRAL MEDICATIONS. The first-line oral antiviral medication for children is acyclovir. Alternatives include valacyclovir and famciclovir, although their use in children had not been approved by the United States Food and Drug Administration as of July 2008. Oral acyclovir is indicated in primary genital HSV infection when treatment is started within 6 days of disease onset and can shorten the duration by 3 to 5 days. In HSV recurrences, initiating oral acyclovir within 2 days of onset shortens the duration only by an average of 1 day. The recommended dose is 1,200 mg/day (maximum of 80 mg/kg per day) for 7 to 10 days in initial infections and for 5 days in recurrences.

Chronic suppressive therapy with oral acyclovir is indicated for patients experiencing recurrence of genital, oral, or ocular HSV infection that involves six or more episodes per year. The recommended pediatric dose is 80 mg/kg per day in three divided doses, with a maximum of 1,000 mg/day for a maximum of 12 months. One study has shown that acyclovir at a dose of 400 mg twice a day chronically can suppress HAEM attacks in most patients. (15)

Acyclovir-resistant strains of HSV must be suspected in patients experiencing worsening disease despite acyclovir therapy, particularly in immunocompromised patients. Foscarnet is the recommended therapy in this case.

PARENTERAL ANTIVIRAL MEDICATIONS. IV acyclovir therapy is reserved for cases having the potential for severe complications. Such situations include any neonate who has HSV infection, mucocutaneous HSV infections in immunocompromised hosts, eczema herpeticum, and HSV encephalitis. The recommended dose is 60 mg/kg per day for 14 days in newborns who have SEM disease and 21 days in other neonatal HSV infections and HSV encephalitis (Table 2).

Acyclovir is known to cause nephrotoxicity. Therefore, it is important to calculate the dose based on ideal

Table 2. Management of Neonatal Herpes

Manifestation	Treatment
Skin, eyes, and mouth	Intravenous acyclovir 60 mg/kg for 14 days
Disseminated and central nervous system	Intravenous acyclovir 60 mg/kg for 21 days
Ocular involvement	Add trifluridine 1%, iododeoxyuridine 0.1%, and vidarabine 3% ophthalmic ointments
Asymptomatic neonates born to mothers who had primary genital infections	Empiric acyclovir therapy pending culture results*
*Not approved by the United States Food and Drug Administration; some controversy exists.	

weight, hydrate the patient well, and monitor urine output and serum creatinine values.

TOPICAL ANTIVIRAL MEDICATIONS. Although commonly prescribed by many physicians, topical antiviral medications such as acyclovir ointment are not recommended to treat most mucocutaneous HSV lesions because such therapy does not reduce the severity or duration of infections in immunocompetent hosts. Topical therapy is recommended in immunocompromised patients because it has been shown to accelerate the healing of lesions.

Ophthalmic antiviral medications, including 1% trifluridine, 0.1% idoxuridine, and 3% vidarabine, are indicated for treatment of ocular HSV and neonatal HSV with SEM involvement.

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Summary

- HSV infection is a multisystem disease characterized by early and often classic skin manifestations. Recognition of the common presentations of mucocutaneous HSV infections can lead to rapid diagnosis and timely treatment.
- The goal of management is to reduce disease severity and prevent recurrences as well as transmission to others through patient education and antiviral therapy.
- HSV1 is associated primarily with infections of the mouth, pharynx, face, eye, and CNS; HSV2 is associated primarily with infections of the anogenital region, although both serotypes may infect any area. (1)
- Based on strong research evidence, transmission of HSV is primarily through exposure to mucocutaneous surfaces with active lesions or viral shedding. (1)
- Based on strong research evidence, the primary method of diagnosis is recognition of the classic presentation of herpetic lesions on mucocutaneous surfaces, but the gold standard of diagnosis is viral culture. (1)
- Based on strong research evidence, empiric treatment of neonatal HSV with acyclovir is recommended if there is a strong clinical suspicion despite the absence of active lesions. (8)
- Based on strong research evidence, suppression therapy with oral acyclovir is beneficial for individuals who have six or more episodes per year of herpes labialis, keratoconjunctivitis, or genital herpes. (8)
- Based on strong research evidence, parenteral acyclovir is recommended in neonatal HSV, HSV in immunocompromised patients, eczema herpeticum, and HSV encephalitis. (8)
- Based on some research evidence, chronic suppressive therapy with acyclovir is beneficial in patients who have HAEM. (14)

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PIR Quiz

Quiz also available online at pedsinreview.aappublications.org.

1. Which of the following statements about HSV is true?
 - A. Anogenital herpes infections always are caused by HSV2.
 - B. Infection is more common in patients who have a higher socioeconomic status.
 - C. Most initial infections do not cause symptoms.
 - D. Orofacial infections should be treated with topical acyclovir.
 - E. Viral shedding lasts longer in reactivation than in an initial infection.
2. You are evaluating a 4-year-old girl who has had blisters around her mouth for 3 days. She has been immunized against VZV but recently was exposed to a child who has chickenpox. Physical examination reveals clusters of vesicles on an erythematous base around her lips. You wonder if this is a primary HSV infection or a mild VZV infection. Of the following, the test that is *least* likely to help you distinguish between these two infections is:
 - A. HSV and VZV antibody titers.
 - B. HSV DFA.
 - C. HSV PCR.
 - D. Tzanck smear.
 - E. Viral culture.
3. You are seeing a 1-day old boy in the newborn nursery because of a rash. He was born at term to a mother who had prenatal care and no history of STIs. He is sluggish at breastfeeding and appears ill. Physical examination reveals several vesicles on his scalp and face. You suspect neonatal herpes infection. Of the following, a true statement regarding this infant and his mother is that:
 - A. Acyclovir should be administered to the infant as soon as possible.
 - B. Administration of acyclovir to the mother during delivery could have prevented this infection.
 - C. Breastfeeding should be stopped to avoid additional spread of the infection.
 - D. His mother likely has a recent recurrence of a genital herpes infection.
 - E. His mother likely was infected with herpes in her first trimester.
4. Which of the following HSV infections is correctly matched with the appropriate treatment?
 - A. Genital herpes and topical acyclovir.
 - B. Gingivostomatitis and IV acyclovir.
 - C. Herpes gladiatorum and oral foscarnet.
 - D. Keratoconjunctivitis and topical vidarabine.
 - E. Neonatal herpes and oral acyclovir.

Herpes Simplex

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