Pediatric Herpes Simplex Virus Infections: An Evidence-Based Approach To Treatment

Abstract

Herpes simplex virus is a common virus that causes a variety of clinical presentations ranging from mild to life-threatening. Orofaryngeal and genital herpes are common disorders that can often be managed in an outpatient setting; however, some patients do present to the emergency department with those conditions, and emergency clinicians should be aware of possible complications in the pediatric population. Neonatal herpes is a rare disorder, but prompt recognition and initiation of antiviral therapy is imperative, as the morbidity and mortality of the disease is high. Herpes encephalitis is an emergency that also requires a high index of suspicion to diagnose. Herpes simplex virus is also responsible for a variety of other clinical presentations, including herpetic whitlow, eczema herpeticum, and ocular herpes. This issue reviews the common clinical presentations of the herpes simplex virus, the life-threatening infections that require expedient identification and management, and recommended treatment regimens.
Case Presentation

A 10-day-old full-term girl is brought to the ED with a rectal temperature of 38.6°C. She has no cough, congestion, runny nose, vomiting, or diarrhea. She is formula-fed and is tolerating her regular feeds. The mother received prenatal care, and the prenatal labs, including Group B Streptococcus, were negative for any pathology. The mother has no reported history of HSV, but she has had a fever and throat pain for the past few days. The infant is sleeping comfortably in her mother’s arms. On examination, the anterior fontanel is soft and flat, and the skin is negative for rash or lesions. Cardiac, respiratory, and abdominal examinations are within normal limits. The infant’s temperature is now 38.7°C rectally. You explain to the medical student working with you on the case that because the baby is < 28 days old and there are no symptoms other than fever, she will require a full sepsis workup, including a lumbar puncture. You inform the medical student that this is standard of care for neonates who present with a fever, and the diagnostics will aid in determining the cause of the fever. Even though the mother has no history of HSV, you have a high index of suspicion for this. The medical student asks you if the baby should be started on acyclovir.

Introduction

Herpes simplex virus (HSV) is a common virus that affects up to 90% of the population by adulthood. Approximately one-third of children contract a primary HSV1 infection by the age of 5 years. In the United States, neonatal HSV disease occurs in approximately 1 in 3200 deliveries, or 1500 new cases annually. Because HSV has many clinical presentations, the emergency clinician must maintain a high index of suspicion for HSV infections and be prepared to offer the appropriate management. The emergency clinician must also be aware of possible complications in the pediatric population as well as the recommended treatments.

Critical Appraisal Of The Literature

A search was performed in PubMed for articles published since 1960 pertaining to children aged < 18 years using multiple combinations of the search terms herpes simplex virus, neonatal herpes, acyclovir, treatment, herpes encephalitis, and genital herpes. The Cochrane Database of Systematic Reviews was also consulted. Articles relevant to pediatric HSV infections were selected and reviewed. Over 300 articles were reviewed, 122 of which were chosen for inclusion in this review, including a number of randomized controlled trials, meta-analyses, and clinical practice guidelines.

Etiology And Pathophysiology

Herpes viruses are enveloped, double-stranded DNA viruses, and their types number > 80. Those that affect humans include herpes simplex virus type 1 (HSV1), herpes simplex virus type 2 (HSV2), human herpesviruses 6 and 7 (HHV6, HHV7), Kaposi sarcoma-associated herpes virus (HHV8), cytomegalovirus, varicella-zoster virus, and Epstein-Barr virus. HSV is transmitted primarily through exposure to skin or mucous membranes that have active lesions. Additionally, transmission may occur through direct contact with saliva or respiratory droplets, or from exposure to mucocutaneous secretions from an individual who is shedding the virus. It should be noted that HSV can be transmitted even if there are no visible sores.

The incubation period for primary or initial HSV1 or HSV2 infection ranges from 2 to 12 days with an average period of 4 days. Following primary infection, there is a period of viral shedding that lasts from 1 to several weeks. Shedding is the process in which the virus may be found on the surface of the skin of patients with no clinical signs. Following the initial or primary infection, the virus typically remains latent within the autonomic ganglia of the host. HSV1 tends to reside within the trigeminal ganglion, while HSV2 commonly resides in the sacral ganglia. While in the ganglia, the virus may replicate without being detected by the host’s immune system.

Clinical symptoms occur when the virus is reactivated. Both internal and external stimuli (eg, stress, fever, menstruation, extremes in temperature, and sunlight exposure) may trigger reactivation. When activated, the virus travels along the sensory nerve and affects the mucocutaneous region that was primarily infected, which is typically the oral area for HSV1 and the genital area for HSV2. Lifelong latency and periodic recurrences are hallmarks of HSV infections.

Disseminated disease may occur when the host is unable to control viral replication. This is usually seen in neonates and immunocompromised hosts. In patients with disseminated disease, the virus invades the lungs, liver, and adrenal glands, and may or may not affect the central nervous system (CNS).

In herpes encephalitis, neurons are destroyed via lytic and hemorrhagic processes that have a predilection for the temporal lobes. In approximately one-third of cases, herpes encephalitis is the result of a primary HSV infection, while the other two-thirds of cases are due to reactivation of the virus.

Epidemiology

Infections with HSV1 are common worldwide. At the time of the most recent National Health and Nutrition Examination Survey (NHANES) completed...
in 2004, two-thirds of the United States population aged > 12 years had an antibody to HSV1, with the seroprevalence higher among females (70.9%) compared to males (64.2%).

Both in the United States and globally, the prevalence of HSV1 infections has been shown to increase consistently with age, reaching approximately 40% by the teenage years and 60% to 90% by older adulthood. Worldwide, the prevalence of HSV1 infection is greater than HSV2 infection. HSV2 is primarily transmitted through sexual contact, so it is not as prevalent in young children. The seroprevalence of HSV2 in patients aged > 12 years is estimated at 21.9%. However, despite efforts to promote safer sex practices, the prevalence of this infection in this population has increased by 30% since the 1970s. Predictors of positive HSV2 status include female gender, black race, greater lifetime number of sexual partners, older age, and low socioeconomic status. Along with the rise of genital HSV2 infection, there has been a rise in the number of genital HSV1 infections, which is most likely secondary to oral-genital contact with a person infected with HSV1.

In the United States, herpes encephalitis is the most common of the lethal encephalitides, with an incidence of 2 cases per million people per year. The disease has a bimodal distribution with the first peak occurring in those aged < 20 years and the second peak occurring in those aged > 50 years. Both sexes are affected equally, and there is no racial predilection. Almost all cases are the result of HSV1 infection, but there have been reports of the occurrence of HSV2 herpes encephalitis. The mortality rate of untreated herpes encephalitis exceeds 70%, and the survivors almost always have neurologic sequelae.

### Neonatal Epidemiology

Seventy percent of neonatal HSV cases are due to HSV2 infection, with the remaining 30% due to HSV1. With the prevalence of HSV2 and the increase in genital HSV1 cases, it is possible that there will be more cases of neonatal HSV in the future. Neonatal HSV infection can be acquired either during intrauterine exposure or during the peripartum and postpartum periods. The estimated incidence of intrauterine HSV infection is 1 in 100,000 deliveries, and HSV2 is thought to account for 90% of these cases. While this is considered to be a rare disorder, intrauterine HSV can lead to significant morbidity and mortality.

Exposure during the peripartum and postpartum periods can be due to maternal infection or an alternative external source; however, as with intrauterine acquisition, mother-to-infant contact transmission remains the highest-risk source for both peripartum and postpartum neonatal infection. Eighty-five percent of infected infants acquire infection in the peri-
**Oral Lesions**

Herpes infections in and around the mouth have many mimickers, including aphthous ulcers, herpangina, and impetigo. Herpes lesions typically lack the honey-colored crust and often follow a dermatomal distribution, which can help distinguish this from impetigo. However, superinfection with *Staphylococcus* or *Streptococcus* is possible and can result in impec- tiginization of the primary herpetic lesion. Aphthous ulcers are similar in appearance to herpetic ulcers, but they can be distinguished by the lack of a vesicular stage and they do not tend to appear on the outside of the lip. Herpangina, which is caused by coxsackieviruses, manifests with yellowish ulcers with a red halo that are found on the buccal surface, gingivae, soft palate, and tonsillar pillars.

**Table 1. Differential Diagnosis Of Herpes Simplex Virus Infections**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Differential Diagnosis</th>
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<tr>
<td>Congenital herpes</td>
<td>• Toxoplasmosis</td>
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<td>• Cytomegalovirus</td>
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<td>• Syphilis</td>
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<td>• Rubella</td>
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<td>Neonatal herpes</td>
<td>• Neonatal sepsis</td>
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<td>• Erythema toxicum</td>
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<td>• Pustular melanosis</td>
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<td>• Varicella-zoster virus</td>
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<td></td>
<td>• Viral pneumonia</td>
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<td>• Viral hepatitis</td>
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<tr>
<td>Herpes labialis and gingivostomatitis</td>
<td>• Impetigo</td>
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<td></td>
<td>• Aphthous ulcers</td>
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<td></td>
<td>• Herpangina</td>
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<td>• Hand, foot, and mouth disease</td>
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<td></td>
<td>• Acute necrotizing ulcerative gingivitis</td>
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<td></td>
<td>• Behcet syndrome</td>
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<tr>
<td>Genital herpes</td>
<td>• Sexually transmitted viral infections</td>
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<td>• Condyloma acuminata</td>
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<td></td>
<td>• Sexually transmitted bacterial infections</td>
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<td>• Syphilis</td>
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<td>• Chancroid</td>
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<td>• Lymphogranuloma venereum</td>
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<td>• Non-sexually transmitted infections</td>
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<td>• Trauma</td>
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<td>• Lichen planus</td>
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<td>• Lichen sclerosis</td>
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<td>• Behcet syndrome</td>
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<td>• Herpes zoster</td>
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<td>• Other</td>
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<td>• Scabies</td>
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<td>Herpes encephalitis</td>
<td>• Abscess/subdural empyema</td>
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<td>• Tumor</td>
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<td>• Reye syndrome</td>
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<td>• Viral encephalitides</td>
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**Genital Lesions**

The differential diagnosis of genital herpes is broad. Primary syphilis, caused by *Treponema pallidum*, presents with painless ulcers, in contrast to the painful lesions of HSV. Chancroid ulcers are pain- ful lesions with a serpiginous border and central exudates caused by *Haemophilus ducreyi*. Ulcerations in Behcet syndrome resemble large aphthous ulcers with irregular borders.

**Encephalitis**

Herpes encephalitis has a broad differential diagnosis, including other viral encephalitides, structural lesions, and vascular disease.

**Prehospital Care**

Emergency medical services (EMS) providers may transport well-appearing patients to the emergency department (ED), but they should be prepared to provide basic and advanced life support for the sick patient with disseminated HSV or HSV encephali- tis. Support of the patient’s airway, breathing, and circulation is critical. Intravenous access should be ob- tained, if needed, and patients should receive isotonic fluid boluses if hemodynamic instability occurs.

**Emergency Department Evaluation**

HSV can cause relatively benign as well as life-threatening diseases. Emergency clinicians must have a high index of suspicion in cases where HSV disease may not be clinically apparent. A thorough history and physical examination is paramount.

**History**

A focused approach to the history may vary based on the patient’s age and presentation. For example, in neonates, maternal history is important, as elements of this may influence suspicion for the risk of HSV transmission.

**Neonates**

When evaluating an ill-appearing or febrile neo- nate, there are several elements of the history that should be investigated. Documentation should include the height of the fever and the method by which it was obtained (rectal, axillary, or tympanic). The family should be questioned regarding how the infant is feeding, as poor feeding can be a sign of illness. Additionally, increased irritability or lethargy should be assessed. The family should be asked if they have noted any rashes on the infant, though these are not always present. The age of the infant is also important, as disseminated disease typically presents at 10 to 12 days after birth, while disease presentation for CNS HSV infection is usually around 16 to 19 days after birth.
The factors that influence the risk of transmission of HSV from mother to baby should be explored. The 5 known risk factors that influence transmission of HSV from mother to baby include: (1) the type of maternal infection (primary vs recurrent); (2) maternal HSV antibody status; (3) duration of time after rupture of amniotic sac membranes; (4) mode of delivery (cesarean section vs vaginal delivery); and (5) integrity of mucocutaneous barriers (use of fetal scalp monitors).3,35-41

During pregnancy, recurrent genital herpes is the most common form of genital HSV infection.3 Recurrent genital herpes is at the highest risk of transmitting HSV to their infant. In a prospective study of over 58,000 pregnant women, Brown et al found that the risk of neonatal transmission was 57% for those with first-episode primary HSV infection versus 25% for first-episode nonprimary HSV infection, and 2% for recurrent genital HSV infections.3 This effect is most likely explained by the lower concentrations of maternal HSV antibodies in women with primary infection versus a higher antibody concentration in women who have recurrent outbreaks.35,38,39 However, 60% to 80% of women who acquire genital HSV during pregnancy are asymptomatic, have no clinical findings to suggest genital HSV infection, and are unaware that they have genital HSV.28,29,39

The duration of the rupture of membranes in the mother may have an effect on the risk of acquiring neonatal infection. The emergency clinician should ask if the mode of delivery was cesarean versus vaginal, as cesarean delivery has been proven effective at preventing transmission of HSV to the neonate.3 The American College of Obstetricians and Gynecologists updated its guidelines for management of genital herpes in pregnancy in 1999.42 The recommendations state that cesarean delivery should be performed if genital HSV lesions or prodromal symptoms are present at the time of delivery in order to reduce the risk of neonatal HSV disease. In the Brown et al study, cesarean delivery significantly reduced HSV transmission rate among women from whom HSV was isolated.3 However, there have been reports of neonatal HSV infection despite cesarean delivery performed before membrane rupture.3

Randolph and colleagues found that 386 cesarean deliveries had to be performed on women with recurrent herpes in order to prevent 1 neonatal infection, which places the cost at more than $1.3 million per neonatal infection prevented.43 In an effort to reduce the number of cesarean deliveries, several studies have evaluated the use of suppressive acyclovir (Zovirax®) therapy to decrease the occurrence of transmission of genital HSV at the time of delivery.44-51 The use of this suppressive therapy has reduced the number of cesarean sections;44,49-51 however, even with acyclovir prophylaxis, transmission of HSV to neonates can still occur.52

The use of fetal scalp monitors has been found to be a risk factor for transmission of HSV due to interruption of the infant’s mucocutaneous barriers.40,41 Therefore, on presentation to the ED, parents should be asked about the use of fetal scalp monitors at the time of delivery, as they may not recall recurrent crusting or blistering over the scalp.

**Oral Lesions**

Acute herpetic gingivostomatitis and herpes labialis are common presentations of primary HSV infection in children. Usually, the onset is quite abrupt and symptoms may persist for 10 to 14 days. A history of eczema, impetigo, or other skin breakdown should be determined, as the oral lesions may be the result of infection secondary to skin breakdown. The presence or absence of fever, irritability, or fatigue should be ascertained, as well as the child’s ability to eat or drink. Due to pain, children may become dehydrated during a herpetic outbreak and they may require fluid resuscitation or admission for hydration. Special attention should be paid to the presence or absence of visual or ocular symptoms, as perioral HSV infection can be a risk factor for ocular infections due to the potential for spread through the trigeminal ganglion.

**Genital Lesions**

The diagnosis of genital HSV is most often made by physical examination. The first episode of a genital outbreak is often accompanied by severe constitutional symptoms, including fever, fatigue, and myalgias. The patient may experience pain, itching, or tingling sensations in the genital region for 24 to 48 hours prior to the development of physical lesions. The emergency clinician should ascertain whether the patient has had an outbreak before, as approximately 90% of patients will have had at least 1 recurrence.4 Attention should be given to the level of pain that the patient is experiencing. Genital lesions are very painful, and this may cause difficulty with ambulation and urination. Urinary retention may be a complication of genital herpes and should be addressed when taking the history.

**Herpes Encephalitis**

The clinical presentation of herpes encephalitis is varied and ranges from mild febrile illness with minimal cognitive impairment to seizures and death. The typical presentation is a flu-like illness with fever and headache, altered mental status, and focal neurologic symptoms. When evaluating a patient with possible herpes encephalitis, the emergency clinician should inquire about the presence of headache, fever, and alterations in consciousness. Focal neurological symptoms may be present, including focal weakness, memory loss, and psychiatric symptoms.
While the presence of vesicular lesions can aid in the diagnosis, approximately 20% of patients never develop cutaneous lesions during the course of the illness. Clinical manifestations of CNS involvement include seizures, irritability, a bulging fontanel, and temperature instability. In contrast to patients with disseminated disease, 60% to 70% of neonates with CNS disease have skin vesicles at some point in the disease course, and vesicular lesions are present in 80% to 85% of cases of neonatal skin, eye, and mouth disease.

Oral Lesions
Herpes labialis will often present with a painful crusted lesion over the outer vermilion border of the lip. Herpetic gingivostomatitis presents with multiple round ulcers or erosions that are commonly seen on the palate, tongue, and gingivae. (See Figure 2.) Diffuse redness and swelling of the gingiva may be seen, along with drooling, halitosis, and anorexia. The lesions may be preceded by a prodrome of generalized malaise and fatigue.

Genital Lesions
Genital herpes classically presents as macules and papules that progress into vesicles, pustules, and ulcers. The ulcers overlying the skin crust over, while those on the mucous membranes heal without crusting. The lesions are painful to the touch. Most patients with genital herpes will also have inguinal lymphadenopathy. Females may have cervical involvement, without any external lesions, especially with first-episode disease. Symptoms are often preceded by a prodrome of fever, headache, malaise, and myalgias.

Herpes Encephalitis
Herpes encephalitis may have subtle physical findings or the findings may be more overt. Typical

Physical Examination
After obtaining a complete history, the physical examination should be conducted with the patient undressed and in a hospital gown. A complete neurological examination should be performed on all patients, including evaluating for irritability, focal neurological deficits, and assessment of the anterior fontanel. The skin should be evaluated for vesicles, ulcers, or other lesions.

Neonates
Infants with congenital HSV are usually diagnosed shortly after birth. CNS, cutaneous, and ophthalmologic involvement is noted in 30% to 50% of intrauterine cases. Other complications include limb abnormalities, hydrops fetalis, visceral involvement, and intrauterine demise.

Neonates with peripartum and postpartum HSV may have a wide variety of clinical presentations, from a well-appearing febrile neonate to a floridly ill-appearing patient. Close attention should be paid to the skin examination, including the former site of a scalp probe. The skin examination may or may not reveal vesicles or other skin changes; however, when present, lesions are characteristically grouped vesicles on an erythematous base. (See Figure 1.) They may occur anywhere on the body, but are usually noted on the scalp, nose, mouth, and eyes. It is important to note that the absence of vesicles does not exclude HSV disease.

Disseminated HSV, HSV with CNS involvement, and HSV skin, eye, and mouth disease have varied presentations. Patients with disseminated disease often present with signs of sepsis, including respiratory collapse, liver failure, disseminated intravascular coagulopathy, and pneumonitis.

Figure 1. Neonatal Herpes Simplex Virus Pustules

Figure 2. Herpetic Gingivostomatitis
presentations include altered mental status, fever, and headache. A thorough neurological examination may reveal focal deficits including unilateral weakness, ataxia, and cognitive problems (eg, memory impairment). Cutaneous findings are uncommon.

### Diagnostic Studies

#### Viral Culture

Viral culture remains the definitive test for the detection of HSV infection outside of the CNS. It has a reported sensitivity of 50% and specificity of nearly 100%.\(^{57}\) The laboratory turn-around time for viral culture is approximately 3 to 7 days.\(^{57}\) When evaluating a neonate for HSV disease, surface viral cultures should be obtained from the mouth, conjunctivae, nasopharynx, and rectum before starting antiviral therapy. Skin lesions and vesicles should also be cultured. However, treatment should be initiated based on clinical suspicion rather than awaiting culture results. Treatment can be tailored, if necessary, based on the results.

Skin or mucous membrane lesions should be unroofed using a sterile needle or scalpel. The base of the vesicle should be swabbed using a Dacron® or rayon swab, and the swab should be firmly rotated over the base of the vesicle. The swab should then be transferred to viral media.\(^{58,59}\) No alcohol or cleansing solutions should be used to clean the lesion prior to swabbing, and calcium alginate swabs should not be used, as they are toxic to HSV.\(^{59}\) With recurrent genital and mucocutaneous lesions, the sensitivity of viral culture is low and declines further as lesions heal.

#### Serologic Testing

Serologic testing can detect HSV1 or HSV2 in people with active disease or with a history of prior infection. Of the numerous tests available, the Western blot is the gold standard. There are also type-specific serologic tests now available that can distinguish between HSV1 and HSV2 antibodies.\(^{60-63}\) For these type-specific tests, the sensitivity has been reported at 90% to 100% and the specificity between 91% and 100%,\(^{60,61,63}\) which is similar to the Western blot. The estimated time to results is 1 to 2 weeks.\(^{57}\)

Type-specific testing can be used as a supplement to antigen testing or viral culture and may be used as a point-of-care test to distinguish patients with HSV-like lesions from patients with HSV. In patients with genital herpes, the patient’s prognosis and counseling needs depend on the herpes serotype (HSV1 or HSV2) causing the infection.\(^{64}\) These tests also allow for the identification of serodiscordant couples (couples in which one partner is HSV2 negative, and the other partner is seropositive). Uninfected females in serodiscordant couples are at risk of acquiring HSV2 during pregnancy and transmitting the virus to the neonate at birth. Serologic testing is of little clinical value in neonatal HSV, since distinguishing between HSV1 and HSV2 does not change the medical management.

#### Polymerase Chain Reaction Testing

Polymerase chain reaction (PCR) testing has revolutionized the diagnosis of HSV and can reliably test cerebrospinal fluid (CSF) and blood for the presence of infection. The sensitivity and specificity of the CSF PCR is > 95%.\(^{65}\) PCR testing is one of the modalities recommended by the United States Centers for Disease Control and Prevention (CDC) for diagnosing genital HSV.

Kimberlin et al compared PCR results to culture-proven HSV disease in 77 neonates and discussed PCR use in neonatal herpes.\(^{66}\) In that study, PCR detected HSV in approximately 25% of infants who were believed to have isolated skin, eye, and mouth disease,\(^{66}\) which suggests that neonatal HSV may represent a disease spectrum rather than 3 distinct categories (CNS disease; disseminated infection; and skin, eye, and mouth disease). Overall sensitivities of CSF PCR testing in neonatal HSV range from 75% to 100%, and specificities range from 71% to 100%.\(^{30,67,68}\) In a study of older patients with biopsy-proven herpes encephalitis, PCR analysis of CSF had a sensitivity of 98% and a specificity of 94%.\(^{69}\)

The broad range of sensitivities in these studies can be explained, in part, by the different methods used in the studies, but false positives and false negatives can occur, so PCR results must be correlated with the patient’s clinical course.\(^{70}\) The presence of high protein levels or blood in the CSF can interfere with PCR assays and cause false-negative results. The detection of HSV in the CSF also decreases markedly after 1 week of antiviral therapy.\(^{69}\) When using the PCR tests on cutaneous lesions, the sensitivity drops to 80% to 90%, but this may vary among laboratories.\(^{57}\)

#### Tzanck Smear

The Tzanck smear is one of the oldest and cheapest tests that can assist in the diagnosis of cutaneous HSV infections, but it is rarely used alone for diagnosis. This testing cannot distinguish between HSV1 and HSV2 and it cannot differentiate between HSV and varicella-zoster virus. PCR testing has been found to be superior to the Tzanck smear; however, the Tzanck smear remains reliable, with a sensitivity of 76.9% and specificity of 100%.\(^{71}\) Due the low sensitivity, the Tzanck smear should not be used in the workup of neonatal HSV, but it may be a quick and useful test in the diagnosis of cutaneous herpes infections.\(^{71}\) In order to collect a Tzanck preparation, the floor of an ulcer is scraped and the obtained material is spread on a glass microscope slide. The slide is then stained with Giemsa stain. If multinucleated giant cells are noted, then the test is positive.
Direct Fluorescent Antibody Testing

Direct fluorescent antibody (DFA) testing uses an antibody tagged with a fluorescent agent that forms an antigen-antibody complex when exposed to an antigen. Slides can be prepared at the bedside for DFA testing using the same technique described for obtaining a viral culture. (See page 7.) Instead of placing the swab in viral culture media, the swab is rolled onto the microscope slide. The cutaneous lesion may also be unroofed and scraped with a spatula and the material collected can then be spread onto a slide. The slide should air dry prior to being sent to the lab. Results can be available in as little as 60 to 90 minutes. The sensitivity of DFA is reported to be 61%, while specificity is 99%.

Lumbar Puncture

A lumbar puncture should be performed on neonates and all patients with suspected CNS involvement. CSF should be sent to the lab for cell count and differential, routine studies to rule out bacterial infection, HSV PCR, and any other disease-screening studies the emergency clinician feels are relevant. Red blood cells and xanthochromia may be seen on CSF studies in patients with CNS HSV infections, but in 5% to 10% of patients, initial CSF studies may be normal. The presence of red blood cells in the CSF is not a feature of neonatal infection, even with CNS involvement. In most cases of herpes with CNS involvement, patients have either an elevated CSF white blood cell count or elevated CSF protein level.

The evaluation of neonates with suspected HSV infection, regardless of category (disseminated; CNS; or skin, eye, and mouth), should include a lumbar puncture with CSF studies in order to rule out CNS involvement. Suspicion for HSV may be heightened based on the results of this testing. In a retrospective study of 5817 neonates, Caviness et al found that CSF pleocytosis was more often seen in bacterial meningitis (5.4%) than in HSV infection (1%). However, in patients with mononuclear CSF pleocytosis, the presence of HSV was twice as likely (1.6%) than it was in bacterial meningitis (0.8%).

Liver Function Tests

In neonates, liver function tests (LFTs) may be helpful in determining possible HSV infection. Elevation of serum aspartate transaminase (AST) levels > 10 times normal have been associated with increased mortality in neonates with disseminated herpes. Elevation of LFTs has also been noted in neonates with disseminated HSV and LFT results may serve as a screening tool for disseminated disease in infants undergoing a sepsis rule-out. Currently, there is no set value for LFTs that correlates with an increased risk of disease.

Imaging Studies

The use of brain imaging may assist in the diagnosis of HSV encephalitis, and magnetic resonance imaging (MRI) is the preferred imaging study. Abnormalities on MRI are found in approximately 90% of patients, with temporal lobe involvement being the most common. In neonates, involvement may be seen in the periventricular white matter. However, early in the illness, the MRI may be normal. Computed tomography (CT) scans are less sensitive than MRI, but they may show changes (such as edema and hemorrhage). These changes often do not appear until 3 to 5 days into the illness when patients are often comatose. In a study of 12 patients, the sensitivity of CT for the detection of herpes encephalitis was 75%, Imaging studies are not routinely performed in neonatal HSV, but when brain imaging is performed, any part of the brain can be involved, and, often, multiple parts of the brain are involved.

Other Studies

In neonates with CNS herpes infection, and in patients with herpes encephalitis, electroencephalography (EEG) is diffusely abnormal. Herpes encephalitis causes characteristic (though not pathognomonic) findings on EEG, including focal slowing, spiking, and lateralizing epileptiform discharges. Similar findings are also noted in neonatal patients with HSV.

Treatment

Neonates

Prior to the use of antiviral therapy, 85% of neonates with disseminated HSV disease and 50% of neonates with CNS disease died within 12 months of diagnosis. Vidarabine (Vira-A®) was the first antiviral medication licensed for use in neonatal HSV. A randomized controlled trial published in 1991 comparing vidarabine with acyclovir found no difference in morbidity or mortality between patients treated with either drug. Despite the lack of evidence of therapeutic superiority, acyclovir became the drug of choice for neonatal HSV due to its more desirable safety profile over vidarabine. Known adverse events of acyclovir use are nephrotoxicity and neutropenia. Acyclovir crystals and precipitate in the renal tubules can cause renal tubular damage and possible renal failure. It is important to ensure that the patient is properly hydrated prior to starting the drug to aid in avoiding nephrotoxicity. Approximately 20% of infants receiving intravenous acyclovir have been noted to develop neutropenia.

The initial studies of acyclovir used a dosage of 10 mg/kg every 8 hours for 10 days. The current recommendation is that neonates with HSV should be treated with intravenous acyclovir at 20 mg/kg/dose every 8 hours. A prospective study of 72 infants with HSV by Kimberlin et al demonstrated...
Clinical Pathway For Management Of Herpes Simplex Virus Infection In Neonates

Neonate presents with any of the following:
• Fever
• Hypothermia
• Irritability
• Lethargy
• Known exposure to HSV
• History of seizures
• More ill than expected
• Vesicles
• Seizures
• Crusting on the scalp

Perform laboratory tests:
• CBC with differential
• Blood culture
• Urinalysis
• Urine culture
• Liver function tests
• Lumbar puncture

Elevated LFTs or CSF mononuclear pleocytosis?

NO
Antibiotics only
(Consider acyclovir if suspicion remains high)

YES
Perform surface cultures and HSV CSF and blood PCR testing (Class I)

Antibiotics AND acyclovir (Class II)

Abbreviations: CBC, complete blood count; CSF, cerebrospinal fluid; HSV, herpes simplex virus; LFT, liver function test; PCR, polymerase chain reaction.

Class Of Evidence Definitions

Each action in the clinical pathway section of Pediatric Emergency Medicine Practice receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probable useful

Level of Evidence:
- Generally higher levels of evidence
- Non-randomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling
a statistically significant higher survival rate in patients treated with the higher dose of acyclovir.\textsuperscript{30} Premature infants may require increased dosing intervals, based on their creatinine clearance abilities.\textsuperscript{84} The duration of therapy is 21 days for patients with disseminated disease or CNS disease and 14 days for skin, eye, and mouth disease.\textsuperscript{38}

The use of empiric therapy in neonates is debated among experts in the field,\textsuperscript{58,85} and the practice of starting empiric antiviral therapy differs among hospitals. There are several considerations when choosing to treat for HSV in this manner. Empirically treating all febrile neonates with acyclovir is costly and not without risks, as infants may experience adverse drug reactions and nephrotoxicity.\textsuperscript{86} Identifying infants at higher risk for disease is difficult, given that most infants with HSV are born to mothers who have no history of herpetic infection.\textsuperscript{35} However, untreated neonatal HSV carries high morbidity and mortality rates, and delaying initiation of acyclovir has been shown to be associated with inhospital death.\textsuperscript{87}

Currently, there are no guideline recommendations regarding when to start antiviral medications in febrile neonates. Caviness et al found that the prevalence of HSV infection was similar to that of bacterial meningitis,\textsuperscript{75} which prompted considerable debate regarding whether all infants undergoing sepsis rule-out should receive empiric acyclovir, since all febrile neonates are empirically covered with antibiotics. One study found that empiric acyclovir use in all infants < 21 days of age captured 90\% of neonatal HSV cases.\textsuperscript{88} Kimberlin et al recommend initiating acyclovir therapy for HSV in neonates undergoing a sepsis rule-out if the following are present: (1) high index of suspicion (presence of vesicles, seizures, elevation of hepatic transaminases); (2) sepsis-like picture, including hypothermia; (3) the infant is more ill than expected; and (4) CSF mononuclear cell pleocytosis is present outside of enterovirus season (May through October).\textsuperscript{58} Long et al concurred with Kimberlin, but limited the age to < 21 days, added CSF mononuclear pleocytosis regardless of season, fever \(\geq 38^\circ\)C without other clear diagnosis, and prurulence or crusting at a former scalp electrode site.\textsuperscript{85}

With the use of high-dose acyclovir (60 mg/kg/day), the 24-month mortality for patients with disseminated neonatal HSV and CNS HSV disease has decreased to 31\% and 6\%, respectively.\textsuperscript{27} However, survivors of neonatal HSV still may have poor outcomes. Kimberlin et al found that approximately 20\% of survivors of disseminated disease and approximately 70\% of those with CNS disease had neurological sequelae 12 months after completion of treatment with acyclovir. Recent trials have supported the use of suppressive therapy with oral acyclovir for 6 months after the completion of standard initial therapy.\textsuperscript{89,90} The current recommendation for antiviral suppressive therapy after completion of standard initial therapy is to treat with 300 mg/m\(^2\)/dose of oral acyclovir 3 times daily for 6 months. The absolute neutrophil count should be checked at 2 weeks, at 4 weeks, and then monthly during the 6-month period to monitor for neutropenia.\textsuperscript{58} Another widely used treatment regimen is 1500 mg/m\(^2\)/dose divided every 12 hours for 12 months.\textsuperscript{91} Please refer to the Pediatric Emergency Medicine Practice 2013 article entitled, “Evaluation Of The Febrile Young Infant: An Update” for additional information.

### Oral Lesions

Antiviral therapy is not routinely used in uncomplicated primary herpetic gingivostomatitis, as weak evidence exists that acyclovir may be effective in reducing the number of oral lesions and/or the development of new lesions.\textsuperscript{92} Oral acyclovir, 15 mg/kg, 5 times daily for 7 days may reduce the severity of disease if it is administered within the first 72 hours of the onset of symptoms.\textsuperscript{93} Oral nonsteroidal anti-inflammatory drugs (NSAIDs) should be used to reduce pain. “Magic mouthwash,” which consists of diphenhydramine, magnesium hydroxide, and/or viscous lidocaine, may be used to reduce pain; however, the use of mouthwashes does not speed recovery.

The treatment of recurrent herpes labialis should be evaluated on an individual basis, with consideration given to the frequency of recurrences, the cost of treatment, and the impairment of quality of life. Treatment options are varied and include topical and oral antiviral therapies. Topical treatment with penciclovir (Denavir\textsuperscript{95}) and docosanol (Abreva\textsuperscript{96}) have been shown to be of some benefit when introduced during the prodromal phase. However, penciclovir has not been approved by the United States Food and Drug Administration (FDA) for use in children aged < 18 years, and docosanol has not been approved for children aged < 12 years.\textsuperscript{5,93} Episodic systemic therapy has also been shown to be effective at reducing the severity and frequency of outbreaks when it is started at the earliest signs of an outbreak,\textsuperscript{94} or within 24 hours. Long-term suppressive therapy may also be used to reduce the number of recurrences.\textsuperscript{92} Table 2 outlines the recommended therapies for herpes labialis.

### Genital Lesions

Antiviral therapy is the mainstay of treatment for symptomatic genital herpes. However, topical analgesia, sitz baths, and counseling on methods to reduce transmission are also important in the clinical management of these patients. Antiviral drugs can aid in controlling the signs and symptoms of herpes outbreaks, but they cannot eliminate the latent virus. This is essential to remember when treating females...
of child-bearing age. The 3 medications proven to have clinical benefit are acyclovir, valacyclovir (Valtrex®), and famciclovir (Famvir®). Management differs, depending on whether the patient has a first outbreak or a recurrent infection. Table 3 outlines the recommended treatments for genital HSV.

**First-Episode**
The first outbreak of genital HSV may cause a prolonged illness with severe genital ulcerations. All patients with first-episode outbreaks should receive antiviral therapy within 72 hours of the appearance of lesions. Treatment may be extended for >10 days if healing is incomplete or if new lesions continue to form. Patients should be counseled to remain abstinent from sexual activity when prodromal symptoms or lesions are present. All persons with genital HSV should be encouraged to inform their current sexual partner that they have genital HSV, and should be educated on ways to reduce HSV transmission to a sexual partner, including proper condom use and suppressive drug therapy.

**Recurrent Episodes**
The majority of patients with genital HSV2 infections will have recurrent episodes, while those with genital HSV1 infections have fewer recurrences. Recurrences may be symptomatic or asymptomatic, but viral shedding occurs during a recurrence, regardless of symptoms. Patients may receive suppressive therapy to prevent outbreaks or episodic therapy to shorten the duration of illness.

Suppressive therapy can reduce the frequency of recurrences by 70% to 80%. Acyclovir, famciclovir, and valacyclovir are equally effective for suppressive treatment of genital herpes. Concerns about transmission to a partner may also play a role when choosing a drug regimen for patients. Corey et al demonstrated that once-daily suppressive therapy with valacyclovir significantly reduced the risk of transmission of genital herpes among HSV2-discordant couples. Safety monitoring of the long-term use of acyclovir, valacyclovir, and famciclovir has been performed and has confirmed that the drugs are safe for long-term use.

**Table 3. Recommended Therapy For Genital Herpes Simplex Infections**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Recommended Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary genital herpes</td>
<td>Acyclovir*</td>
</tr>
<tr>
<td></td>
<td>• 400 mg PO tid for 10 days</td>
</tr>
<tr>
<td></td>
<td>or</td>
</tr>
<tr>
<td></td>
<td>• 200 mg PO 5 times/day for 10 days</td>
</tr>
<tr>
<td></td>
<td>• Children aged &lt; 12 y: 40-80 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>• divided over 3-4 doses for 5-10 days</td>
</tr>
<tr>
<td></td>
<td>• Max daily dose: 1000 mg</td>
</tr>
<tr>
<td></td>
<td>Famciclovir†</td>
</tr>
<tr>
<td></td>
<td>• 250 mg PO tid for 10 days</td>
</tr>
<tr>
<td></td>
<td>Valacyclovir</td>
</tr>
<tr>
<td></td>
<td>• 1 g PO bid for 10 days</td>
</tr>
<tr>
<td>Recurrent genital herpes (episodic therapy)</td>
<td>Acyclovir*</td>
</tr>
<tr>
<td></td>
<td>• 200 mg PO 5 times/day for 5 days</td>
</tr>
<tr>
<td></td>
<td>or</td>
</tr>
<tr>
<td></td>
<td>• 800 mg PO bid for 5 days</td>
</tr>
<tr>
<td></td>
<td>• Max daily dose: 80 mg/kg divided q6-8h</td>
</tr>
<tr>
<td></td>
<td>Famciclovir†</td>
</tr>
<tr>
<td></td>
<td>• 125 mg PO bid for 5 days</td>
</tr>
<tr>
<td></td>
<td>Valacyclovir</td>
</tr>
<tr>
<td></td>
<td>• 500 mg PO bid for 3 or 5 days</td>
</tr>
<tr>
<td></td>
<td>or</td>
</tr>
<tr>
<td></td>
<td>• 1000 mg PO qd for 5 days</td>
</tr>
<tr>
<td>Recurrent genital herpes (suppressive therapy)</td>
<td>Acyclovir*</td>
</tr>
<tr>
<td></td>
<td>• 400 mg bid</td>
</tr>
<tr>
<td></td>
<td>• Children aged &lt; 12 y: 300 mg/m²/dose tid</td>
</tr>
<tr>
<td></td>
<td>• Max daily dose: 1000 mg</td>
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<tr>
<td></td>
<td>Famciclovir†</td>
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<td>• 250 mg bid</td>
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<td></td>
<td>Valacyclovir</td>
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<td></td>
<td>• 500 mg qd</td>
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<td>or</td>
</tr>
<tr>
<td></td>
<td>• 1000 mg qd</td>
</tr>
</tbody>
</table>

Abbreviations: bid, 2 times per day; q, every; qd, 1 time per day; PO, by mouth; tid, 3 times per day.

*Non-weight-based dosing recommendations for patients aged ≥ 12 years.
†Dosing recommendations for patients aged ≥ 18 years.
should be provided a prescription for a drug regimen to initiate on their own. In order for episodic treatment to be effective, patients must initiate therapy within 1 day of the onset of lesions or during the prodrome that some patients experience. Episodic therapy does not reduce the risk of viral transmission. If transmission is a concern, patients should be placed on suppressive therapy.

**Encephalitis**
The drug regimen for the treatment of herpes encephalitis has changed over the years, with acyclovir now being the treatment of choice. Whitley et al published a randomized controlled trial of 208 patients with brain-biopsy-proven herpes encephalitis and found that acyclovir was more effective than vidarabine in decreasing mortality rates. The recommended dose of acyclovir is 10 mg/kg every 8 hours for 21 days.

**Vaccine**
Presently, there is no effective vaccine to prevent HSV1 or HSV2 acquisition. There have been several attempts to develop a vaccine for genital herpes, and some appear promising. An HSV2 glycoprotein-D-subunit vaccine with alum and 3-O-deacylated-monophosphoryl lipid A was found to be effective in women who were seronegative for HSV1 and HSV2 prior to receiving the vaccine. In another randomized double-blind trial testing the same vaccine in seronegative women, an efficacy of 58% against HSV1 genital disease was found, but the vaccine lacked efficacy against HSV2. With continued research, an effective vaccine may be possible in the coming years.

**Special Circumstances**

### Eczema Herpeticum
Eczema herpeticum, also known as Kaposi-Juliusberg varicelliform eruption, is a dermatologic emergency presenting as a diffuse HSV skin infection, typically in children or young adults with eczema. It is characterized by a diffuse eruption that quickly develops from vesicles and pustules that become crusted over. Fever, malaise, and regional lymphadenopathy are often present. The severity is variable, ranging from a mild transient disease to a fulminant fatal disorder. Mortality rates prior to the advent of antiviral medications were estimated to be between 10% and 50%, but today, mortality rates are < 10%. Early identification and treatment of eczema herpeticum is important, as it may progress to disseminated disease if untreated. Diagnosis is often made clinically and verified with PCR, viral culture, and/or DFA. Acyclovir is the treatment of choice, and either oral or intravenous acyclovir can be used, depending on the severity of the illness. The recommended intravenous dosage is 15 to 30 mg/kg/day divided into 3 doses for 7 to 10 days. The recommended oral dose is 30-60 mg/kg/day divided into 3 doses for 5 to 10 days. Antibiotics should be provided to patients in whom bacterial superinfection is suspected. Topical steroids have not been shown to be associated with worse outcomes or increased length of stay in children with eczema herpeticum, and they may be used for treatment, especially as combination therapy for control of eczema flare-ups. Ophthalmology should be consulted emergently if any lesions are near the eye or along the trigeminal nerve, as keratoconjunctivitis can occur, which can lead to blindness.

### Herpes Gladiatorum
First reported in the 1960s, herpes gladiatorum is an HSV1 infection that typically occurs in athletes who participate in contact sports. It is also known as “wrestler’s herpes,” “mat pox,” or “scrum pox.” Athletes are inoculated with HSV1 through abraded skin and typically develop cutaneous eruptions on the face, neck, ears, and upper extremities within 2 weeks of the contact with the virus. Other symptoms include facial pain, fever, and lymphadenopathy. Treatment includes oral antiviral medications and restriction from sports until resolution of the outbreak. Primary outbreaks should be treated with 10 to 14 days of antiviral medications, while recurrent outbreaks require 5 days of therapy. Any person in contact with an infected individual during the 3 days prior to the outbreak should be isolated from contact sports for 8 days and should be examined prior to return to play. Some evidence suggests that the prophylactic use of valacyclovir during sports camps or a competitive season may minimize the risk of transmission.
**Herpetic Whitlow**

Herpetic whitlow is a self-limited cutaneous infection that typically occurs on the distal phalanx of the fingers, and it often affects healthcare workers, children with primary oral herpes, and adolescents and adults with genital herpes. The estimated incidence is 2.4 cases per 100,000 people per year.\(^{114}\) Herpetic whitlow is most commonly transmitted via direct contact with a herpetic lesion, autoinfection from nail biting, or contact with HSV-infected bodily fluids.\(^{2,93,94,114}\) The most common clinical presentation is pain at the affected fingertip. With primary infection, fever and malaise may also occur. Within 1 to 2 days after the onset of pain, small vesicles may coalesce to form bullae. (See Figure 4.) After 10 to 14 days, the skin lesions become crusted and peel, revealing normal skin. Scarring rarely occurs with herpetic whitlow. Diagnosis is often made clinically, but can be confirmed with a Tzanck smear measurement of antibody titers to HSV, viral culture, or DFA. Incision and drainage of the lesion should be avoided, as this may cause increased duration of infection and increased risk of further infection.\(^{115}\) The area should remain covered with a dressing to prevent transmission, and patients should be provided with analgesics. Data regarding the efficacy of topical or oral antiviral medications are limited, but in patients with severe disease, treatment may be beneficial.\(^{114}\)

**Ocular Herpes**

Ocular herpes is one of the most common causes of corneal blindness in the United States.\(^{2,94}\) Infection may cause unilateral or bilateral conjunctivitis. There are various types of clinical expression of this disease, each with specific examination findings and treatment. Epithelial keratitis is the most common form of ocular HSV infection and accounts for 50% to 80% of cases.\(^{116}\) Patients with epithelial keratitis may have dendritic lesions noted on fluorescein testing. Index of suspicion for ocular herpes should be high if any lesion is noted along the trigeminal nerve. Urgent referral to an ophthalmologist for diagnosis and treatment is optimal. Treatment varies with presentation and should be dictated by ophthalmology specialists, when available. Dendritic or epithelial keratitis can be managed with topical antiviral agents, such as vidarabine and trifluridine (Viroptic\(^\circ\)) for 10 to 14 days, or with oral acyclovir 400 mg 5 times daily for 10 days.\(^{117}\)

**Controversies And Cutting Edge**

Although the vast majority of neonatal HSV cases are acquired in the peripartum period from contact with secretions from the maternal genital tract, occasionally, neonatal infection is acquired postnatally. There have been multiple case reports of neonatal HSV in male infants following out-of-hospital Jewish ritual circumcision.\(^{118-120}\) In Jewish tradition, male infants are circumcised 8 days after birth by a mohel in a ritual known as a bris. Mohels receive specific training on the procedure. In a small subset of the Orthodox Jewish community, the Mohel orally sucks the blood after cutting the foreskin, an act known as mezizah.

In New York City between 2000 and 2011, 11 male newborns were found to have HSV infection following an out-of-hospital Jewish ritual circumcision. Ten of the 11 newborns were hospitalized, and

**Time- And Cost-Effective Strategies**

- **Do not initiate empiric antiviral therapy on all infants.** There are several considerations when choosing whether or not to empirically treat for HSV. Empirically treating all febrile neonates with acyclovir is costly and is not without risks, as infants may experience adverse drug reactions and nephrotoxicity.\(^{86}\) Identifying infants at higher risk for disease is difficult, given that most infants with HSV are born to mothers who have no history of herpetic infection.\(^{35}\) When evaluating an infant for a sepsis rule-out, there are many opinions regarding when to start empiric acyclovir. A suggested algorithm for starting acyclovir in neonates is included on page 9.

- **Combine viral surface cultures for neonatal herpes.** Viral swabs from the conjunctiva, mouth, nasopharynx, and anus (anal swab should be performed last) may be collected with single swab and placed in a viral transport media tube. The presence or absence of viral replication is the key indicator of HSV.
1. “The mother of the ill-appearing 15-day-old infant did not have a history of herpes, so the infant most likely has a bacterial infection rather than neonatal herpes.”

Almost two-thirds of women who acquire genital herpes during pregnancy are asymptomatic and have no clinical findings to suggest genital HSV infection, as they have never had an HSV outbreak, nor have their partners had an outbreak. 28,29,39,122

2. “The lumbar puncture was not bloody, so the patient probably does not have HSV.”

While the presence of red blood cells and xanthochromia on a lumbar puncture may be seen on CSF studies in patients with HSV encephalitis or CNS involvement, 5% to 10% of patients have normal CSF studies. Red blood cells in the CSF is not a feature of neonatal infection, even with CNS involvement. 27 PCR should be completed on the CSF of all patients suspected of having HSV encephalitis or CNS involvement. 73 In most cases of herpes with CNS involvement, patients have either an elevated CSF white blood cell count or elevated CSF protein level, which may heighten the emergency clinician’s suspicion for CNS herpes infection. 74

3. “The 3-day-old infant had pustules on the skin, so he probably has neonatal herpes.”

The presence of pustules on an infant does not necessarily mean the patient has HSV. Pustular melanosis and erythema toxicum are both benign pustular eruptions that can mimic HSV.

4. “The baby was born via cesarean delivery, so herpes does not need to be ruled out.”

While cesarean delivery has successfully reduced the number of neonatal herpes cases, HSV may be transmitted to an infant despite cesarean delivery.

5. “I did not see any dendrites on the fluorescein examination, so the patient does not have ocular herpes.”

All patients who are suspected of having ocular herpes should be evaluated by an ophthalmologist. Findings may be subtle, and those with expertise in the evaluation of the cornea should be involved when there is any clinical concern for ocular HSV infection.

6. “The child had swelling and pain near the fingertip, so I performed an incision and drainage.”

Routine incision and drainage is not recommended in patients with herpetic whitlow. Herpetic whitlow is a self-limited disease. Vesicles may be unroofed to help relieve symptoms, but deep incisions should be avoided.

7. “No lesions are visible on the external genital examination, so the patient does not have a herpes outbreak.”

Patients with herpes outbreaks may not have lesions visualized on external examination. If lesions are not noted, a pelvic examination should be performed to evaluate for the presence of cervical lesions.

8. “The Tzanck prep was negative on the skin lesion of the 15-day-old infant, so HSV was ruled out.”

While the Tzanck prep may be a relatively reliable test for cutaneous lesions, it does not definitively rule out neonatal herpes. If suspicion is high for neonatal herpes infection, infants require the following testing: (1) CSF for indices; (2) HSV PCR and bacterial culture; (3) viral culture swabs from the base of any vesicles as well as swabs from the mouth, conjunctiva, nasopharynx, and rectum; (4) HSV PCR on whole blood; and (5) LFTs.

9. “The CT scan on the febrile teenager with altered mental status was negative, so HSV PCR does not need to be sent on the CSF.”

CT scans are less sensitive than MRI, but they may show changes (such as edema and hemorrhage) in patients with herpes encephalitis. However, early in the illness, CT and MRI may be normal, so clinical suspicion should guide management and workup.

10. “LFTs are not part of the routine sepsis rule-out. They play no role in the evaluation of febrile infants.”

Elevation of serum aspartate transaminase levels > 10 times normal have been associated with increased mortality in neonates with disseminated herpes. 27,32,76 Elevation of LFTs have been noted in neonates with disseminated HSV 75,77 and LFT levels may serve as a screening tool for disseminated disease in those infants undergoing a sepsis rule-out.
have greatly improved the efficacy and tolerability of treatment of HSV infections, prevention of disease, either by reducing transmission rates or by the development of a vaccine, should remain the primary goal.

**Case Conclusion**

A full sepsis workup was completed on the patient. Her CSF differential was notable for a mononuclear cell pleocytosis, and her LFTs were elevated. You started her on empiric antibiotics, and you explained to the medical student that the elevated LFT results and mononuclear cell pleocytosis increased your suspicion for neonatal HSV, so you also started empiric acyclovir. Blood and urine cultures were negative at 48 hours, but her CSF HSV PCR was positive. She was admitted to the hospital and continued on intravenous acyclovir for 21 days. After that point, she was discharged home on suppressive oral acyclovir.

**References**

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study will be included in bold type following the references, where available. The most informative references cited in this paper, as determined by the author, will be noted by an asterisk (*) next to the number of the reference.


17. Roberts CM, Pfister JR, Spear SJ. Increasing proportion of herpes simplex virus type 1 as a cause of genital herpes infection in college students. Sex Transm Dis. 2003;30(10):797-800. (Retrospective; 499 patients)


64. Scuolar A. Using the evidence base on genital herpes: optimising the use of diagnostic tests and information provision. Sex Transm Infect. 2002;78(3):160-165. (Review)


97. Fife KH, Crumpacker CS, Mertz GJ, et al. Recurrence and resistance patterns of herpes simplex virus following cessation of > or = 6 years of chronic suppression with acyclovir. A retrospective study; 1 patient.


115. Wilhelmus KR. Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis. Cochrane Database Syst Rev. 2010(12):CD002898. (Meta-analysis; 106 trials, 5872 eyes)


4. Which of the following statements regarding genital herpes is TRUE?
   a. The majority of cases are caused by HSV1.
   b. External lesions may not be noted during an outbreak.
   c. Episodic treatment can prevent transmission to sexual partners.
   d. There is no indication for hospitalization for genital herpes.

5. Which of the following tests is important for the evaluation of neonatal HSV?
   a. CSF PCR
   b. Surface cultures
   c. Liver function tests
   d. All of the above

6. Which of the following is the most reliable test for the diagnosis of neonatal HSV involving the CNS?
   a. Type-specific serology
   b. Viral culture
   c. Tzanck smear
   d. PCR assay

7. What is the recommended initial standard therapy dose of acyclovir to treat neonatal herpes?
   a. 10 mg/kg/dose every 8 hours
   b. 20 mg/kg/dose every 8 hours
   c. 60 mg/kg/dose every 8 hours
   d. 30 mg/kg/dose every 8 hours

8. The recommended duration of standard initial treatment for neonatal CNS HSV infection is:
   a. 10 days
   b. 14 days
   c. 21 days
   d. 30 days

9. In herpes encephalitis patients, there is no difference in outcome for patients treated with vidarabine versus patients treated with acyclovir.
   a. True
   b. False

10. A lesion noted along the distribution of the trigeminal nerve should raise concern for ocular herpes infection.
    a. True
    b. False
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Needs Assessment: The need for this educational activity was determined by a survey of medical staff, including the editorial board of this publication; review of morbidity and mortality data from the CDC, AHA, NCHS, and ACEP; and, evaluation of prior activities for emergency physicians.

Target Audience: This enduring material is designed for emergency medicine physicians, physician assistants, nurse practitioners, and residents.

Goals: Upon completion of this activity, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical ED presentations; and (3) describe the most common medicolegal pitfalls for each topic covered.

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