

Herpes Simplex Virus

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

1. Describe the epidemiology of herpes simplex virus (HSV) and the distinctive epidemiologic features of HSV type 1 and type 2.
2. Characterize the pathogenesis, diagnosis, treatment, and outcome of HSV infections in the neonate.
3. Explain the variety of clinical manifestations and methods of diagnosis of HSV infections in older children and adolescents.
4. Discuss the appropriate potential prevention and therapy of HSV infections in infants, children, and adolescents.

Background

Herpes simplex infections have various presentations, depending on the immune status, the age of the host, and the route of transmission. Herpes simplex viruses (HSVs) are enveloped, double-stranded DNA viruses. The two serotypes of HSV are classified as HSV-1 and HSV-2. Infections with HSV-1 usually involve the face and skin “above the waist,” although HSV-1 also can cause genital infection. Infections with HSV-2 usually involve the genitalia and skin “below the waist” in sexually active adolescents and adults. Most HSV disease in neonates is due to HSV-2. HSV-2 also causes oral lesions in approximately 25% of the infected population. Throughout this article, we categorize HSV disease by the specific host.

Epidemiology of HSV Infections

Neonatal

The incidence of neonatal HSV infection is estimated at 1 per 3,000 to 20,000 live births. Between 20% and 40% of infants infected with HSV are born preterm. In the United States, approximately 75% of neonatal infections are due to HSV-2, with the remainder due to HSV-1. HSV infection develops in 33% to 50% of exposed infants born vaginally to mothers who have primary genital infection. The risk to an infant born to a mother shedding HSV as a result of reactivated infection is much lower (0 to 5%). More than 75% of infants who acquire HSV infection have been born to women who had no signs or symptoms suggestive of HSV infection before or during pregnancy. Occasionally, postnatal transmission may occur from a caregiver who has oral or hand lesions.

Neonatal HSV infection may occur between birth and 4 weeks of age. Neonatal disease may present as: 1) disseminated disease involving multiple organs, most prominently the liver and lungs and possibly with a central nervous system (CNS) component; 2) disease localized to any area of the skin, eyes, and mouth (SEM); or 3) localized CNS disease. Disseminated disease has the earliest age of onset, often during the first postnatal week; CNS disease has the latest age of onset, usually between the second and third weeks after birth.

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Mucocutaneous

The incubation period for HSV infection occurring beyond the neonatal period ranges from 2 days to 2 weeks. Children living in crowded situations contract HSV-1 more commonly during the first few years of life; infection typically occurs later in life among individuals from less crowded living conditions.

Genital

Genital HSV-2 infection usually results from sexual intercourse; genital infection with HSV-1 results more frequently from oral-genital contact. Often the primary genital infection is asymptomatic, but some individuals may develop frequent clinical recurrences. Why recurrence occurs in some patients and not in others is not well understood. It has been noted that genital infections due to HSV-2 are more likely to recur than genital HSV-1 infections.

Transmission

HSV may be transmitted from both symptomatic and asymptomatic individuals and may occur with either primary or recurrent infections. Infection with HSV-1 usually results from direct contact with infected oral secretions or lesions. Infection with HSV-2 usually results from direct contact with infected genital secretions during sexual activity, via contact with genital lesions, or with asymptomatic viral shedding. Infection also may be acquired during delivery, particularly in infants of mothers who have ruptured membranes greater than 4 to 6 hours.

The incubation period for HSV infection ranges from 2 to 14 days for children beyond the newborn age. Experimental data show that the greatest concentration of HSV is shed during primary symptomatic infection and the least during asymptomatic recurrent infections. However, the more typical case of transmission is from an individual who is shedding HSV asymptotically. Patients who have primary gingivostomatitis or genital herpes typically shed virus for a longer period than those who have recurrent infections. Shedding with an initial HSV infection is typically 1 week, but may be longer. In contrast, shedding with recurrent infections is shorter in duration, often just 3 to 4 days. Intermittent asymptomatic reactivation of oral and genital herpes is common and persists for life. In previously infected children, the prevalence of asymptomatic viral shedding is 1%.

Clinical Manifestations (Table 1)

Neonatal

Approximately 25% of neonatal HSV cases are disseminated, 35% present as CNS disease, and 40% affect the SEM, although the disease types overlap clinically. In many neonates who have disseminated or CNS disease, skin lesions do not develop or the lesions appear late. The absence of skin lesions does not exclude the diagnosis of neonatal HSV infection, which makes this a challenging clinical diagnosis. It is critical to think of herpes simplex infection in the baby who is discharged from the nursery but presents as a sick infant before 3 weeks of age. Over the past 20 years, because of continued delay in diagnosis, physicians have not shortened the interval between the onset of symptoms and the initiation of antivirals (mean, 6 d), although early initiation of acyclovir has been shown to improve outcomes in both morbidity and mortality.

Mucocutaneous Disease in Older Infants and Children

Most primary HSV infections are asymptomatic in children and infants beyond the neonatal period, with HSV present in both symptomatic and asymptomatic individuals. Infection with HSV-1 usually results from direct contact with infected oral secretions or lesions. Infection with HSV-2 usually results from direct contact with infected genital secretions or lesions through sexual activity. Genital infections caused by HSV-1 in children can result from autoinoculation of virus from the mouth, whereas sexual abuse should be considered in prepubertal children who present with genital HSV-2 infections. Genital HSV isolates from children can be typed to differentiate between HSV-1 and HSV-2, although the reliability of this typing depends on laboratory experience. The mucocutaneous manifestations of herpes simplex may present as herpes labialis, gingivostomatitis, eczema herpeticum, herpetic whitlow, herpetic conjunctivitis, herpes gladiatorum, and genital herpes.

Herpes labialis, the most conspicuous form of recurrent mucocutaneous herpes, often occurs in association with stress. This herpetic infection of the lips frequently recurs with the trigeminal ganglion as the site of latency for the virus. When symptomatic, recurrent herpes labialis manifests as single or grouped vesicles in the perioral region, usually on the vermilion border of the lips, which commonly are referred to as cold sores or fever blisters.

Gingivostomatitis, which is the most common clinical manifestation in children and young adults, usually is caused by a primary HSV-1 infection. Affected children have an ulcerative enanthem involving the gingival and

Table 1. Clinical Manifestations and Treatment of Herpes Simplex Virus Disease

Type of HSV Infection	Population Age	Treatment Options	Outcome
Neonatal SEM CNS Disseminated	Birth to 4 wk	Acyclovir IV	Excellent Significant morbidity and mortality Significant morbidity and mortality
Labialis	Child to adolescent	Acyclovir PO	Excellent
Gingivostomatitis	Infant, toddler, child	Consider acyclovir PO	Excellent
Eczema herpeticum	Toddler to adolescent	Consider acyclovir PO	Good
Herpetic whitlow	Child to adolescent	Consider acyclovir PO	Excellent
Herpes gladiatorum	Adolescent		Excellent
Genital	Adolescent	Acyclovir, famciclovir, or valaciclovir PO	Good
Conjunctivitis/keratitis	Infant to adolescent	Trifluridine, idoxuridine, or vidarabine topical**	Variable
Encephalitis	Infant to adolescent	Acyclovir IV	Variable
Immunocompromised host	Infant to adolescent	Acyclovir IV or foscarnet IV	Variable

SEM=skin, eye, mucous membrane disease; CNS=central nervous system; IV=intravenous; PO=oral; **=ophthalmology consultation required

mucous membranes, which makes eating and drinking painful. The mouth lesions often are accompanied by fever, fussiness, and tender submandibular adenopathy, and the child may become dehydrated if he or she is unable to drink because of pain.

Eczema herpeticum is a febrile condition consisting of a widespread eruption of vesicles that rapidly become umbilicated pustules, particularly in areas of eczematous involvement. Herpetic whitlow consists of single or multiple vesicular lesions, usually on the distal part of a finger. Herpetic whitlow may occur as a complication of primary oral or genital herpes by inoculation of HSV via a disruption in the epidermal integrity or by direct inoculation of virus into the hand through occupational (eg, nursing) or some other type of exposure. Herpes gladiatorum describes mucocutaneous HSV infections of the thorax, ear, face, and hands among wrestlers, with transmission of HSV facilitated by trauma to the skin sustained during wrestling.

Vesicular or ulcerative lesions of the male or female genitalia or perineum characterize genital herpes. Most cases are due to HSV-2, but genital herpes can be caused by HSV-1. The frequency of HSV-2 infection correlates with the number of sexual partners and the acquisition of other sexually transmitted diseases. Transmission of genital herpes can be reduced substantially with the use of condoms, which is one in a myriad of reasons to encourage sexually active adolescents to use condoms.

Regardless of the form of mucocutaneous herpetic infection, after primary infection, HSV persists for life in

a latent form. Reactivation of latent virus most commonly occurs in the absence of symptoms.

Conjunctivitis and keratitis can result from primary or recurrent HSV infection and usually are due to autoinoculation from oral shedding.

CNS Manifestations of HSV

Beyond the neonatal period, HSV encephalitis can result from primary or recurrent infection; is usually due to HSV-1; and can be associated with fever, alterations in the state of consciousness, seizures, focal neurologic findings, and personality changes. Approximately 0.5% to 5% of children who have herpetic infection can develop herpes encephalitis. HSV encephalitis frequently has an acute onset with a fulminant course, leading to coma and death in untreated patients. It is characterized by a relatively low pleocytosis of the cerebrospinal fluid (CSF) (white blood cell count of 25 to 1,000/mcL [0.025 to $1 \times 10^9/L$]), with a predominance of lymphocytes. Approximately 50% of cases have evidence of erythrocytes in the CSF.

HSV infection also can cause meningitis with nonspecific clinical manifestations that usually are mild and self-limited. HSV meningitis (in contrast to encephalitis) is rare, does not require antiviral therapy, and is associated with genital HSV-2 infection. HSV infection has been reported with a number of unusual CNS manifestations, including Bell palsy, atypical pain syndromes, trigeminal neuralgia, ascending myelitis, and postinfectious encephalomyelitis.

In immunocompromised patients, even local disease can extend rapidly in the region or be disseminated extensively, including visceral involvement. Early aggressive antiviral therapy of localized disease may prevent dissemination in these very susceptible hosts. Neonates should be considered to be immunocompromised patients, a concept that adds to the understanding of the severity of this infection in the neonatal population.

Diagnosis

A high level of clinical suspicion is necessary to diagnose HSV infection, particularly in the neonate who does not exhibit classic vesicular lesions. For neonates who have vesicular lesions, HSV infection should be diagnosed presumptively and acyclovir therapy initiated pending confirmatory laboratory testing. Clinical diagnosis of herpes labialis, gingivostomatitis, and genital herpes usually is apparent, and culture for HSV is not necessary. Atypical HSV infections, including cases in immunocompromised patients, may require culture and antiviral susceptibility testing to guide antiviral therapy. An ophthalmologist should be consulted for diagnosis, management, and follow-up of the patient who has HSV conjunctivitis and keratitis.

For patients who have herpes encephalitis, an electroencephalogram (EEG) often is useful for supportive diagnosis by demonstrating an abnormality, particularly in the temporal lobe region. A specific EEG pattern of periodic lateralizing epileptiform discharges is highly suggestive of CNS herpes infection. Magnetic resonance imaging of the CNS demonstrates typical abnormalities of edema or hemorrhagic necrosis, particularly in the temporal lobe region involving the white matter.

Diagnostic Tests (Table 2)

Of the sites routinely cultured for HSV, skin or conjunctival cultures consistently provide the greatest diagnostic yields regardless of disease classification, with more than 90% of cultures being positive. HSV infection is confirmed best in the laboratory by isolation of virus in tissue culture or by demonstration of HSV antigens or DNA in scrapings from lesions.

CULTURE OF THE ORGANISM

HSV grows readily in cell culture, particularly when obtained from the fluid of an unroofed vesicle. Special transport media are avail-

able for specimens that cannot be inoculated immediately onto appropriate cell culture media. Cytopathogenic effects typical of HSV usually are observed 1 to 3 days after inoculation, making relatively rapid identification achievable with good culture techniques. Conversely, cultures that remain negative by day 15 are considered negative. Most CSF cultures for HSV in both neonates and older patients who have encephalitis due to HSV are negative. Specimens for cultures can be obtained from skin vesicles, mouth or nasopharynx, conjunctivae, urine, blood, stool or rectum, and CSF.

ANTIGENIC DETECTION

Direct fluorescent antibody staining of vesicle scrapings or enzyme immunoassay of HSV antigens is as specific as viral culture but often less sensitive. These tests frequently are performed by laboratories to type culture isolates rather than as a means of primary identification.

Serology has little value in the diagnosis of neonatal HSV infection. Cross-reactivity is high between HSV-1 and HSV-2. The high prevalence of HSV infections, particularly HSV-1, can result in seropositivity for HSV immunoglobulin (Ig)G in many infants. Infants who have perinatally acquired infection may be seronegative. The presence of specific IgM antibodies may be more helpful in diagnosing congenital infection. These antibodies usually appear in the first 4 weeks after birth and can persist for many months.

NUCLEIC ACID DETECTION

Polymerase chain reaction (PCR) of CSF is a sensitive method for detecting HSV DNA in very experienced laboratories and is of particular value for evaluating CSF specimens from cases of suspected herpes encephalitis. Because most CSF cultures for HSV are negative in infants who have localized CNS infection and in older patients who have HSV encephalitis, PCR amplification

Table 2. Herpes Simplex Diagnostic Tests

Type of Diagnostic Tests	Suitable Specimens
Culture	Conjunctivae, nasopharynx, skin, rectal swab, blood
ELISA	Conjunctivae, nasopharynx, skin, rectal swab, blood; confirmatory test of virus from culture sites
DFA	Conjunctivae, nasopharynx, skin, rectal swab, blood; confirmatory test of virus from culture sites
PCR	Cerebrospinal fluid
Tzanck preparation	Skin scraping
ELISA=enzyme-linked immunosorbent assay; DFA=direct fluorescent antibody; PCR=polymerase chain reaction	

of herpes simplex DNA in the CSF has been useful for diagnosis of CNS infections.

TZANCK PREPARATION

This test has low sensitivity and is useful only if positive as a rapid diagnostic test indicating the presence of a DNA virus, which includes both herpes and varicella. Histologic examination of lesions identifies the presence of multinucleated giant cells and eosinophilic intranuclear inclusions typical of HSV. However, this test is not specific for HSV.

Treatment

Neonatal

During prenatal visits and labor, all women should be asked about previous and current signs and symptoms consistent with genital herpes infection, and they should be examined carefully for evidence of genital infection. Cesarean delivery performed in women who have clinically apparent HSV infection may reduce the risk of neonatal HSV infection from 50% to 5% if performed within 4 to 6 hours of membrane rupture, but it is less likely to reduce the neonatal infection rate if performed later. Many experts and these authors recommend cesarean delivery whenever the birth canal is infected, even if membranes have been ruptured for 6 hours or more. A maternal history of genital HSV infection with normal findings on maternal genital examination at delivery has *not* been a classic indication for cesarean delivery. All invasive monitoring (eg, scalp monitors) should be avoided when possible in infants of women who have active genital herpes infection.

For infants born to mothers who have a primary genital infection, the risk of infection may exceed 50%. There is a variance in expert opinion on the management of infants who are born to mothers who have a primary genital infection with HSV. Some experts recommend empiric acyclovir treatment at birth after HSV cultures have been obtained; other experts suggest obtaining HSV cultures 24 to 48 hours after delivery and initiating intravenous acyclovir therapy only if HSV is recovered from these cultures. If a neonate develops a rash or clinical symptoms suggestive of sepsis, cultures should be obtained and acyclovir therapy initiated immediately. The management of exposed asymptomatic infants who are delivered vaginally of mothers who have active genital lesions that are known to represent recurrent disease includes culture of lesions (nasopharynx, conjunctivae, stool, umbilicus) and careful observation for signs of infection, including the development of vesicular lesions of the skin, jaundice, respiratory distress, or seizures. If

cultures are negative and there continues to be no evidence of infection, careful observation remains the standard. With neonatal HSV infection occurring as late as 4 weeks after delivery, parents and physicians must be vigilant and carefully evaluate any rash or other symptoms that may be caused by HSV because affected children will not stay in the nursery for an extended period. Both mothers and their infants should be managed by using contact precautions during delivery and postpartum.

All neonatal HSV infections should be treated with intravenous acyclovir. Neonates in whom HSV infection is limited to the SEM usually have an excellent outcome when treated with intravenous acyclovir. Although most neonates treated for HSV encephalitis survive, the majority suffer substantial neurologic sequelae. Approximately 50% of neonates who have disseminated disease die despite antiviral therapy.

The dosage of acyclovir is 60 mg/kg per day in three divided doses given intravenously for 14 days for SEM disease and for 21 days if disease is disseminated or involves the CNS. This dose often is referred to as high-dose acyclovir because the previously recommended dosing was 15 mg/kg per day. A large multicenter study suggested a small decrease in morbidity among patients treated with high-dose acyclovir. The drawback is the increased occurrence of neutropenia, which requires monitoring of the white blood cell count twice weekly during the course of therapy. If a patient displays significant neutropenia, either the acyclovir dose should be decreased or granulocyte-stimulating factor should be added to the regimen. Additionally, vigorous hydration and monitoring of renal function is required during acyclovir therapy.

Both SEM and CNS disease can recur after discontinuation of parenteral acyclovir, which mandates close follow-up and occasional use of long-term suppressive or intermittent acyclovir therapy. The value of long-term suppressive or intermittent acyclovir therapy for neonates who have SEM disease currently is being investigated. These authors and others recommend a lumbar puncture at the end of the proposed therapy when the CNS is involved to ascertain that the PCR for HSV from the CSF is negative. If HSV is still present in the CSF, antiviral therapy may be continued until the CSF becomes sterile.

Infants who have ocular involvement due to HSV infection require close evaluation and treatment by a pediatric ophthalmologist. The children should receive a topical ophthalmic drug (1% to 2% trifluridine, 1% iododeoxyuridine, or 3% vidarabine) as well as parenteral antiviral therapy.

Mucocutaneous

In a small study, early therapy with oral acyclovir has been noted to have a modest clinical effect in children who have primary gingivostomatitis. Among adults who have recurrent herpes labialis, oral acyclovir may be moderately useful if administered in the early stages, with reduction of lesions and symptoms by 1 to 2 days. Oral acyclovir is most useful in this situation if initiated at the onset of symptoms, including the characteristic perioral “tingling” that occurs prior to the development of the classic vesicular lesion. Topical acyclovir is ineffective. Generally, care is supportive for pain relief and to assure adequate hydration.

Ocular

Eye lesions in older children should be treated in consultation with an ophthalmologist who has pediatric experience. Several DNA inhibitor drugs, such as 1% to 2% trifluridine, 1% iododeoxyuridine, or 3% vidarabine, have proven efficacy for topical therapy of superficial keratitis. Topical corticosteroids are contraindicated in suspected HSV conjunctivitis, although an ophthalmologist may choose to use corticosteroids in conjunction with antiviral drugs to treat locally invasive infections. For children who have recurrent ocular lesions, oral suppressive therapy with acyclovir (2 mg/kg q 6 h) may be of benefit.

Genital

For primary genital herpes, oral acyclovir therapy, initiated within 6 days of the onset of disease, shortens the duration of illness and viral shedding by 3 to 5 days. Valacyclovir and famciclovir do not seem to be more effective than acyclovir, although they offer the advantage of less frequent dosing. Intravenous acyclovir is indicated for patients who have a severe or complicated primary infection that requires hospitalization. Topical acyclovir (5%) ointment for primary genital herpes infection has minimal effects on the duration of viral shedding and symptoms and is not recommended. Systemic or topical treatment of primary herpetic lesions does not affect the subsequent frequency or severity of recurrences.

The usual site of latency for genital herpes is the sacral ganglia. Antiviral therapy has a minimal effect on recurrent genital herpes. Oral acyclovir therapy initiated within 2 days of the onset of symptoms shortens the mean clinical course by approximately 1 day. Topical acyclovir is not beneficial for immunocompetent hosts. In some cases of adults who have frequent genital HSV recurrences (at least six episodes per year), daily oral acyclovir suppressive therapy is effective for decreasing

the frequency of symptomatic recurrences. Daily acyclovir is used for approximately 1 year, and the recurrence rate is reassessed. This approach has not been studied in adolescent patients.

Immunocompromised

Immunocompromised patients who have systemic HSV infection or extensive mucocutaneous disease require intravenous acyclovir therapy until there is no further progression of disease and no new lesions. Strains of HSV resistant to acyclovir have been isolated from immunocompromised persons receiving prolonged treatment with acyclovir. Under these circumstances, progression of disease may be observed despite acyclovir therapy. Foscarnet is the drug of choice for disease caused by acyclovir-resistant HSV isolates.

Prognosis

Neonatal

Recent studies show that the mean time (6 d) between the onset of HSV disease symptoms and the initiation of therapy has not changed significantly over the past 20 years. Among patients who have CNS disease, mortality is associated with prematurity ($P=.05$) and seizures ($P=.06$) at the initiation of therapy. Among patients who had disseminated HSV disease treated with acyclovir at 30 mg/kg per day, mortality was associated with aspartate aminotransferase elevations of more than 10 times the upper limit of normal at the time of therapy initiation. Mortality also was associated with lethargy at the initiation of antiviral therapy for patients who had disseminated disease. In a recent large natural history study, among surviving patients who had known morbidity, 98% of patients who had SEM disease, 30% of those who had CNS disease, and 75% of those who had disseminated disease had normal development at 12 months of age. More than 50% died with disseminated HSV infection, and approximately 10% had severe morbidity at 1 year of age. In neonatal HSV CNS disease, more children who had HSV-2 were severely affected than those who had HSV-1 disease (70% versus 40%). Conversely, mortality was more common in disseminated disease due to HSV-1 and in HSV-2 CNS disease.

Mucocutaneous

The prognosis for mucocutaneous herpetic infections is excellent in otherwise healthy individuals. These self-limited, nonlife-threatening illnesses may improve slightly more rapidly with the use of systemic antivirals, depending on the specific syndrome.

Ocular

The prognosis for ocular disease depends on the underlying immune status of the patient and the amount of involvement at the time of presentation. There can be significant scarring if the infection is invasive, even at a local level.

Genital

Genital herpes generally decreases in both severity and frequency of recurrences over an individual's lifetime. There is less viral shedding with each recurrence. Transmission continues to be a concern, but it often can be prevented by use of condoms. Aseptic meningitis syndrome due to a complication of the reactivation of HSV genital infection is a rare but possible late manifestation of the disease.

CNS

Older children who have herpes encephalitis may have significant neurologic sequelae, including seizures and mental retardation, even when treated with acyclovir.

Immunocompromised

Immunocompromised patients may develop disseminated HSV disease that often is not responsive to acyclovir. In addition, it can be difficult to contain localized disease in immunocompromised patients despite administration of systemic acyclovir.

Summary

HSV infections vary in presentation and management among neonates, children, and adolescents. Early consideration and treatment for neonatal disease is essential. Clinical diagnosis alone usually is adequate for most of the mucocutaneous HSV presentations in childhood and adolescence. The ease of antiviral therapy administration

has improved, although delays in diagnosis and the overwhelming clinical manifestations of invasive HSV disease make this a devastating illness, particularly in the newborn and immunocompromised patient.

Suggested Reading

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PIR Quiz

Quiz also available online at www.pedsinreview.org.

6. Which of the following statements regarding herpes simplex (HSV) infections in neonates is *true*?
 - A. A neonate is most likely to acquire congenital herpes if his or her mother has a recurrence of infection at the time of delivery.
 - B. HSV-2 causes all neonatal herpes infections.
 - C. Most neonates who are born with congenital herpes are born to mothers who have signs and symptoms of active disease at the time of delivery.
 - D. Neonatal HSV encephalitis usually presents within the first 3 to 5 days after birth.
 - E. With appropriate treatment, neonates who have limited SEM involvement typically have an excellent outcome.

7. Which of the following statements regarding genital herpes is *true*?
 - A. Genital infections due to HSV-1 are more likely to recur than those due to HSV-2.
 - B. HSV meningitis without encephalitis is associated with HSV-2 genital infections.
 - C. The amount of viral shedding increases with each recurrence of genital HSV.
 - D. The use of condoms has not been shown to reduce the incidence of transmission of primary HSV infections.
 - E. Treatment of genital HSV infections with acyclovir has been shown to reduce the incidence of future recurrences greatly.

8. You are a resident working at a pediatric tertiary care center. You are evaluating a 21-day-old baby whose mother has no history of herpes infections. The baby has two vesicles on his abdomen. He appears septic and soon has a generalized tonic-clonic seizure. Within a few hours, he requires intubation. Even though the maternal history is negative, you suspect herpes encephalitis. Which of the following diagnostic tests is *most* likely to confirm your diagnosis?
 - A. Cerebrospinal fluid erythrocyte count.
 - B. Direct fluorescent antibody staining of vesicle scraping.
 - C. Polymerase chain reaction for HSV DNA of cerebrospinal fluid.
 - D. Tzanck preparation of vesicle scraping.
 - E. Viral culture of cerebrospinal fluid.

9. Of the following, the correct pairing of herpes manifestation and treatment of choice is:
 - A. Conjunctivitis and topical corticosteroid drops.
 - B. Disseminated neonatal disease and intravenous acyclovir.
 - C. Genital lesions and topical 5% acyclovir ointment.
 - D. Gingivostomatitis and topical 5% acyclovir ointment.
 - E. Neonatal SEM involvement and oral acyclovir.

10. Which of the following statements regarding the diagnosis and treatment of HSV infections in children is *true*?
 - A. A Tzanck smear of a skin lesion differentiates between HSV and varicella.
 - B. An electroencephalographic reading showing epileptiform activity in the temporal lobes confirms the diagnosis of herpes encephalitis.
 - C. The diagnostic test of choice for older children who have herpes encephalitis is serology.
 - D. Valacyclovir is the treatment of choice for acyclovir-resistant infections in immunocompromised persons.
 - E. Viral culture gives the greatest diagnostic yield in herpes infections without encephalitis.