

Neonatal Herpes Infection

Infants with vague and generalized symptoms of malaise, irritability, poor feeding, or jaundice during the first few weeks of life present an ongoing challenge to the health care community as a whole and transport personnel in particular. The overwhelming majority of infants who present with these symptoms have relatively benign health problems.

However, a small population of infants progress from these vague symptoms to fulminant infection and death. Herpetic infections, particularly infections in the intrauterine and neonatal period, can be physically destructive to the affected child and emotionally devastating for families. Although drug regimens have been developed for the treatment of human herpetic infections, diagnosis and treatment in infants continue to be delayed. This delay in diagnosis is related to factors such as variability of disease presentation, minimization and denial of symptoms, and knowledge deficits on the part of infant caregivers.

This article defines and differentiates the symptoms and sequelae of the eight currently identified forms of human herpes viruses. Also discussed are the common progression of herpetic infection, current drug regimens, mechanisms to isolate and protect the patient and transport staff, and the potential impact of herpetic infection on the family unit of the neonate.

Case Study

A vehicle pulled into the ambulance bay of the emergency department, and a frantic mother called for assistance. "My baby is not breathing!" Initial assessment of the child revealed a cyanotic infant with a respiratory rate of less than 10 breaths/min and a weak, palpable, femoral pulse greater than 200 beats/min. Assisted ventilation with a resuscitation bag and 100% oxygen were provided. The infant's weight was measured at 5 kg. Oral tracheal intubation was performed, and an intraosseous infusion was initiated; 40 mL/kg warm normal saline was infused (20 mL/kg \times 2), with improvement of capillary refill and restoration of weak peripheral pulses. Blood glucose measured with a bedside glucometer was 6 mg/dL. The infant's hypoglycemia was treated with a 2-mL/kg bolus of D10W, and serum glucose was rechecked to confirm resolution of hypoglycemia. After blood, urine, and cerebral spinal fluid collection for bacterial cultures, intravenous ampicillin and gentamicin were initiated. The child was admitted to the pediatric intensive care unit (PICU) for further care.

In the 48 hours after admission, the child continued to have temperature instability, declining liver function, and focal seizures. Although no skin lesions were detected and the patient's mother denied any exposure to herpetic infection, a herpes polymerase chain reaction (PCR) assay was sent from previously collected spinal fluid. In addition, the patient's skin, rectum, oral cavity, and eyes were swabbed for herpes surface cultures. Intravenous acyclovir was initiated on PICU day 2

without resolution of symptoms. On PICU day 5, the child developed pulmonary hemorrhage that could not be effectively treated. The infant was pronounced dead 35 minutes after initiation of resuscitation attempts. Resulting cultures and autopsy showed a disseminated herpes simplex 2 infection with hepatic necrosis and multiple cerebral lesions.

The Pathology of Herpes

Derived from the Greek root word *herpein* (to creep), herpes is a series of virulent infections that produce a varied pattern of expression. Because of the ability of all eight of the known herpes viruses to shed in the absence of active or recognizable disease, containment and prevention of virus proliferation has been unachievable.

During the active reproduction of viruses such as herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2), specific DNA sequences are replicated that may or may not cause host cell death. Throughout dormant periods after infection (latency), the virus is present in the viable target cells and is stored in sensory axons that connect to the point of initial entry of the virus.¹ The latent virus can be reactivated by stressors such as physical or emotional exertion, fever, ultraviolet light exposure, or active tissue destruction.²

Viral reactivation can present as an active infectious process or a subclinical infection (viral shedding or asymptomatic infection). More than 60% of new HSV-2 and 30% of HSV-1 infections have no clinical symptoms.³ The infectious cycle of herpes consists of primary infection (patients that do not have active antibodies to the presenting infection), possible nonprimary infection (patient develops a first onset of the herpes prodrome of symptoms with antibodies previously present), and recurrent infectious outbreaks intermixed with periods of latency.⁴ Although thousands of herpes viruses have been isolated, eight strains are currently known to be human pathogens. Table 1 lists and describes them.

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According to the Centers for Disease Control and Prevention,⁵ "immunologic changes during pregnancy, primary depression of certain aspects of cell mediated immunity such as decreased levels of helper T-cells can lead to fetal development without rejection... Some infections are severe in pregnancy... Transplacental infection with viruses have been associated with abortion, congenital anomaly, and mental retardation."

The contrast between primary and recurrent infections with herpes viruses is an important consideration in the discussion of congenital and neonatal herpetic infections. During primary viral infections an increase occurs in both the quantity of the virus shed and the duration of the excretion period. Pregnancy results in an absence of maternal antibodies to suppress the

vention will have an effect. In contrast, a "null" hypothesis proposes no relationship. For example: Family satisfaction with transport will not increase with an increase in time spent with the family before transport.

The null hypothesis is an important statistical concept and is used as the basis for the statistical analysis to be used at the conclusion of the study. This will be discussed in greater detail in a future part of this series.

Taking the Next Step

Now you have a research question that is well defined, refined, and highly specific. However, it may not be completely finalized. You have started the planning process that is the most important part of any research study. In research endeavors, more time should be spent on planning rather than rushing into actually performing the study. The next step is to research the topic further, including a systematic review of the literature relevant to your focused research question. The process of reviewing the literature will be discussed in an upcoming part in this series.

Congratulations on taking the first and most important step to better understanding the medical literature, or to becoming a researcher yourself. Although there are many roadblocks in the research process, there is tremendous personal satisfaction in performing credible research. This series will try to help with each of the steps and point out some of the pitfalls. In addition, if you want to read about this subject in greater depth, a number of excellent textbooks are available. Listed below are some of the best for the beginning researcher.

References

1. Melnyk, BM, Fineout-Overholt E. Evidence-Based Practice in Nursing & Healthcare. Philadelphia: Lippincott Williams & Wilkins; 2005.
2. Burns N, Grove SK. The Practice of Nursing Research: Conduct, Critique & Utilization. 5th ed. Philadelphia: Saunders; 2004.
3. Hulley SB, Cummings SR, Browner WS, Grady D, Hearst N, Newman TB. Designing Clinical Research: An Epidemiologic Approach. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2001.

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with referring and receiving institutions can help transport staff develop an infection control plan that encompasses herpes virus and all other potential mediums and strains of chemical and biological toxins.

The Emotional Impact

The social stigma associated with the word and diagnosis of *herpes* is undeniable. Social mores associated with the disease, general isolation during the identification of infectious organisms, the potential need for transport of the infant to a neonatal specialty center, and possible parental feelings of guilt and shame all impact the family unit. Long-distance transport also may isolate the parent(s) from support systems.

The neonatal transport team members should anticipate parental anxiety during the diagnosis process and disease progression. The transport team may be the only familiar faces that parents encounter as they arrive at the neonatal specialty center. By identifying potential needs of the family unit, assisting in making appropriate referrals, and maintaining confidentiality, the transport team can assist the family in this stressful period.

Conclusion

Caregivers involved in neonatal transport should include herpetic infection in the differential diagnoses for all infants with suspected sepsis. The naturally immunocompromised state of infancy, the subtle presentation of signs and symptoms in the infant, and the increased prevalence of herpetic infections in the general population combine to make herpes diagnosis and treatment challenging. Despite progression of neonatal intensive and emergency care and interventions, 25% of infants with disseminated herpes infections die of their disease.

References

1. Stevens JG, Cook ML. Latent herpes simplex virus in spinal ganglia of mice. *Science* 1971;173:843-845.
2. Kiberlin D. Neonatal herpes simplex infection. *Clin Microbiol Rev* 2004;17:1-13.
3. Simon H. Herpes simplex. *MDConsult* 2003:1-20.
4. Klein R. Clinical manifestations and diagnosis of herpes simplex virus type 1 infection. *Up to Date-Online* 2005;13.3.
5. American Academy of Pediatrics. Herpes simplex. In: Pickering LK, editor. *Red Book: 2003 Report of the Committee on Infectious Diseases*. 26th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2003:344-353.
6. Bolyard E. Guidelines for infection control in health care personnel. *Am J Infect Control* 1998;26:407-463.
7. Whitley RJ, Nahmias AJ, Visintine AM, Fleming CL, Alford CA. The natural history of herpes simplex virus infection of mother and newborn. *Pediatrics* 1988;66:489-494.
8. Brown ZA, Wald A, Morrow RA, Seike S, Zeh J, Corey L. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. *JAMA* 2003;289:203-209.
9. Coletti JE, Homme JL, Woodridge DP. Unsuspected neonatal killers in emergency medicine. *Emerg Med Clin North Am* 2004;22:1-19.
10. Kimberlin DW, Lin CY, Jacobs RF, Powell DA, Corey L, Gruber WC. Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. *Pediatrics* 2001;108:230-238.
11. Micromedex monograph 126. 2005. Thompson Healthcare Inc., Licensed to the University of Michigan Medical Center.

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Table 1. Types of Human Herpes Viruses

Type 1	
Common designation	HSV 1, herpes labialis, cold sores, fever blisters
Common age of onset	Early childhood
Presence in the general population	Up to 80% of the American population.
Mode of transmission	Close physical contact, especially with oral secretions. Viral shedding can lead to unknowing transmission to others.
Isolation procedure	Standard precautions
Additional information	Although commonly referred to as "oral herpes," it is not uncommon to have alternative types of herpetic viral infections in locations other than the standard location of inflammation. Retrospective studies demonstrate that only 20% to 25% of patients with HSV-1 antibodies and 10% to 20% of those with HSV-2 antibodies have a history of oral-labial or genital infections. ^{1,4} Ten percent of genital herpes outbreaks are cultured to be HSV-1. ²
Type 2	
Common designation	HSV 2, genital herpes
Common age of onset	Age at which sexual activity is initiated
Presence in the general population	According to the Centers for Disease Control and Prevention, the male-to-female transmission is most effective, accounting for the seropositive status of males of 20% vs. female infection rate of 5% in the general US population. ³ However, men have a higher risk of viral reactivation than women. Fewer than 10% of the 60 million people in the United States infected with herpes simplex are aware they are infected. ⁴
Isolation procedure	Standard precautions
Additional information	With changes in traditional sexual practices (such as an increased participation in oral sexual activity), there is variation in the location of outbreaks of the infection commonly referred to as "genital herpes."
Type 3	
Common designation	HHV-4, varicella zoster, chickenpox
Common age of onset	Primarily an infection of childhood
Presence in the general population	Prior to the onset of mass immunization in the United States, there were approximately 4 million infections a year, 11,000 hospital admissions, and up to 100 deaths a year after infection. ⁵
Mode of transmission	Respiratory/airborne contamination, direct contact, and possible aerosolization of vesicular fluid
Incubation period	Average incubation period is 14-16 days.
Period of active shedding of virus	2 days before the onset of vesicular rash until the lesions are completely crusted over (usually 4-5 days).
Congenital infection	May produce a spectrum of responses from seropositive infants without notable effects to significant presentation of symptoms such as fetal varicella syndrome. This syndrome consists of a combination of maladies, including intrauterine growth retardation, cutaneous scarring, limb hypoplasia, microcephaly, cortical atrophy, and a combination of ocular defects. ⁶
Isolation procedure	Airborne and contact precautions
Additional information	Immunization does not eliminate the potential of infectious viral activation after varicella exposure. Varicella vaccine has been demonstrated 70%-90% effective at preventing infection and 95% effective at preventing severe infection. ⁷
Type 3B	
Common designation	Herpes zoster, shingles
Common age of onset	Most common in elderly and immunocompromised patients
Presence in the general population	Up to 15% will have an outbreak during their lifetime. ⁸
Period of active shedding of virus	During reactivation process of the virus
Isolation procedure	Cover active lesions; use contact isolation for patients for whom covering of active lesions is not possible. ⁹
Additional information	Although not as virulent as primary varicella zoster, the active virus can be transmitted and infect others with primary varicella ⁶
Type 4	
Common designation	HHV-4, Epstein-Barr Virus (EBV)
Common age of onset	Variable
Presence in the general population	90%-95% of the adult population ⁹
Mode of transmission	Saliva and moist mucous membranes
Period of active shedding of virus	Up to 10 years after initial infection ²
Isolation procedure	Contact isolation
Additional information	Although this herpes virus is associated with mononucleosis in Western civilization, HHV-4 has direct correlation as a causative agent of Burkitt's lymphoma on the African continent and nasopharyngeal carcinoma in the geographical population of Asia ²
Type 5	
Common designation	HHV-5, cytomegalovirus (CMV)
Common age of onset	Variable

Table 1. Types of Human Herpes Viruses— Continued

Type 5— Continued	
Presence in the general population	Infection rates increase from 15% of adolescents to 50%-80% of the adult population older than age 40. ^{2,9}
Mode of transmission	Contact with infectious secretions, sexual contact, breast milk, infected organ transplant, and through blood transfusions
Incubation period	Unknown
Period of active shedding of virus	Variable. Viral shedding frequently resumes during periods of immunosuppression.
Congenital infection	5% to 20% of infants born to mothers with primary CMV infection will be symptomatic. These children have a mortality rate of 9% and severe neurologic morbidity in 80% of surviving infants. ¹⁰
Isolation procedure	Standard precautions
Additional information	Cytomegalovirus is the leading causative agent of deafness and the second leading cause of mental retardation (second only to Down's syndrome) in the United States. ¹¹ Infection is most frequently spread through seeding of mucous membranes of the mouth and nose by hands that are ineffectively cleansed. ⁹ Viral loads of CMV-positive blood transfusions are high enough to produce systemic inflammation and organ dysfunction in infants. ²
Type 6	
Common designation	HHV-6, human B-lymphotropic virus
Common age of onset	Usually a mild, self-limiting illness of children ¹⁰
Presence in the general population	Widespread in adult population (> 90%) ¹⁰
Mode of transmission	Contact with saliva, moist mucous membranes, and possible respiratory transmission
Incubation period	14 days
Period of active shedding of virus	Unknown
Isolation procedure	Contact precautions recommended at this time
Additional information	HHV-6 has two forms. Form 6A is the causative agent in roseola infantum ¹⁰ Form 6B is the primary infectious agent correlated to mononucleosis. ² Although current research does not support the correlation, HHV-6 has a weak association with chronic fatigue syndrome, hepatic failure, multiple sclerosis, and malignancies affecting the lymphatic tissues.
Type 7	
Common designation	HHV-7
Common age of onset	Usually in early childhood. Infection peaks around 3 years old. ^{2,10}
Presence in the general population	70% to 95% of adults are seropositive.
Mode of transmission	Primarily through saliva. Virus also found in breast milk, cervical secretions, and bone marrow.
Incubation period	Unknown. The primary infection is usually asymptomatic. ¹⁰
Period of active shedding of virus	Assumed active shedding of virus with all contacts.
Isolation procedure	Contact isolation
Additional information	There is a correlation with the onset of febrile seizures in primary infections of HHV-7. This herpes virus may be a cofactor in reactivation of other viral infections in immunosuppressed individuals. ¹⁰
Type 8	
Common designation	Kaposi's sarcoma-associated herpes virus (KSHV)
Common age of onset	Varied
Presence in the general population	Up to 30% of US blood donor population. Most common in children, those who engage in male/male sexual partnerships, organ transplant recipients, and the immunocompromised.
Mode of transmission	Unknown, probable source is saliva
Incubation period	Onset of active disease is common years after initial infection.
Period of active shedding of virus	Unknown
Congenital infection	Varied, up to 6% of American children from birth to 38 months were found to be seropositive for KSHV. ¹²
Isolation procedure	Standard precautions
Additional information	Type 8 is also associated with an increased incidence of malignancies such as lymphomas, disorders of the lymph system, and in limited studies solid tumors, primary pulmonary hypertension, and sarcoidosis. ¹²

1. Klein R. Clinical manifestations and diagnosis of herpes simplex virus type 1 infection. *Up to Date-Online* 2005;13.3.

2. Hunt R. Virology-herpes viruses. *Microbiology Immunology On-Line*. University of South Carolina School of Medicine, 2004.

3. Albrecht M. Clinical manifestations and diagnosis of genital herpes simplex virus infection. *Up to Date-Online* 2005;13.3.

4. Simon H. Herpes simplex. *MDConsult* 2003;1-20.

5. Centers for Disease Control and Prevention. Decline in annual incidence of varicella, Selected states, 1990-2001. *MMWR Morb Mortal Wkly Rep*. 2003;52:884.

6. American Academy of Pediatrics. Herpes simplex. In: Pickering LK, editor. *Red Book: 2003 Report of the Committee on Infectious Diseases*. 26th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2003:344-353.

7. Centers for Disease Control and Prevention. Clinical questions. 2005. Available at www.cdc.gov/nip/diseases/varicella/faqs-clinic-disease.htm.

8. Bolyard E. Guidelines for infection control in health care personnel. *Am J Infect Control* 1998;26:407-463

9. Schmidt DS. Cytomegalovirus infection. Washington, DC: National Center for Infectious Diseases; 2005:1-5.

10. Tremblay C. Cytomegalovirus infection in pregnancy. *Up to Date-Online*. 2005;13.3.

11. Hoff M. Silent plight. *University of Minnesota News* 2005 Spring.

12. Casper C, Corey L. Disease associations of human herpes virus 8 infection. *Up to Date-Online*. 2005;13.3.

infectious organism. **Two thirds of women who are infected with herpes during pregnancy are asymptomatic during pregnancy.**² Sixty percent to 80% of HSV-infected infants are born to mothers who deny (or are unaware of) exposure to contacts positive for herpetic infection or have no current signs or symptoms of herpes infection.⁶ Mothers with primary infection during pregnancy have a 30% to 50% infant infection rate. In comparison, recurrent maternal herpes infection poses less than a 2% fetal risk of infection.⁷

Although considered a standard of care, cesarean section delivery in the setting of active herpes infection does not offer complete protection against infant herpes simplex. Transplacental infection and environmental contacts continue to act as vectors of infection.

The incidence of neonatal herpes simplex infection ranges from 1 in 3000 to 1 in 20,000 live births in the United States (or approximately 3000 cases per year).^{8,9} A wide spectrum of clinical symptoms are seen with neonatal HSV infection. Symptoms may include febrile illness, intractable or focal seizure activity, jaundice, premature birth, skin and mucous membrane manifestations, and sepsis. Herpes simplex has an incubation period of 5 to 21 days. This variable and prolonged incubation produces delays in diagnosis, as infants may not present with symptoms of infection until days 2 to 35 of life.⁹

Intrauterine infection does occur, with an incidence of 1 in 300,000 live births. Transplacental infection usually presents with a constellation of symptoms, including cutaneous findings, ocular impairment, and neurologic involvement.⁵

The presentation of herpes simplex in infancy can be divided into three distinct patterns of infection:

- **Disseminated disease.** A global herpetic infection with major impact on multiple organ systems. Twenty-five percent of neonatal herpes simplex infections are disseminated in presentation. Mortality is 90% if untreated and 31% with current antiviral regimens.⁹ Note that 20% of infants with disseminated herpes simplex do not develop classic herpetic cutaneous lesions during their illness or course of care.²
- **Central nervous system (CNS) herpes simplex infection.** Thirty-five percent of infants with herpes simplex infection present with a focal neurologic infection. Signs and symptoms such as temperature instability, bulging fontanel, encephalitis, infant irritability, respiratory depression, and arrhythmias can be the presenting factor in such infections. Infant morbidity and mortality is associated with neurologic consequences of the meningitis/encephalitis and resulting loss of function. Mortality from herpetic CNS infection ranges from 6% to 50%, depending on treatment mode.^{2,9}
- **Skin, mouth, and eye infections with herpes simplex.** This is the most common form of neonatal herpes simplex, accounting for 40% of the documented infections.² If left untreated, localized lesions such as cutaneous vesicular lesions, keratitis, and chorioretinitis can broaden to systemic infection. With implementation of current treatment protocols, this is the least virulent of the modes of infant herpetic simplex infection.

Treatment

Mortality in the pre-antiviral era was 90% for disseminated disease and 50% for CNS disease.⁶ In addition to the increases

in the effectiveness and availability of neonatal emergency and intensive care, institution of high-dose antiviral therapy with acyclovir has reduced mortality to 31% for disseminated disease and 6% for CNS disease.¹⁰ Acyclovir (Zovirax, GlaxoSmithKline, Research Triangle Park, NC) has become the standard antiviral treatment for herpes simplex virus, herpes zoster, and varicella-zoster virus.² Nucleosides, such as acyclovir, inhibit viral DNA replication and penetrate most body tissues, including the cerebral spinal fluid, spine, and brain, with little effect on healthy cells.³ According to the recommendations of the American Academy of Pediatrics, acyclovir should be administered to all neonates with herpes simplex infection regardless of clinical findings.⁸ Of note, antiviral-resistant strains of herpes virus have been documented in 0.1% to 0.7% of immunocompetent hosts. This rate increases to 4% to 14% in immunocompromised patients.² Repeating herpes surveillance screening at the conclusion of therapy to rule out the possibility of continued subclinical infection is advisable.

Treatment Guidelines for Acyclovir

Current recommendations for acyclovir administration are outlined below.

- The dosage of acyclovir is 60 mg/kg per day in three divided doses, given intravenously over 1 hour's duration for 14 days if the disease is limited to the skin, eyes, and mouth and for 21 days if the disease is disseminated or involves the CNS.⁸
- Typical half-life of acyclovir in the neonatal population is 4 hours, but this depends on renal function as the drug is excreted in the kidneys.¹¹
- According to Micromedex,¹¹ "Precipitation of acyclovir crystals in renal tubules can occur if the maximum solubility of free acyclovir (2.5 mg/mL at 37°C in water) is exceeded or if the drug is administered by bolus injection. Ensuing renal tubular damage can produce acute renal failure. Abnormal renal function (decreased creatinine clearance) can occur as a result of acyclovir administration and depends on the state of the patient's hydration, other treatments, and the rate of drug administration. Concomitant use of other nephrotoxic drugs, pre-existing renal disease, and dehydration make further renal impairment with acyclovir more likely."
- Acyclovir can decrease plasma concentrations of phenytoin and valproic acid, decreasing seizure thresholds.¹¹

Infection Control and Transport

Transport care providers should be aware that most of the patients they encounter will have and potentially be shedding some form of herpes virus. As listed in Table 1, there is a large variability of infective vectors. Uncertainty of disease-specific routes of transmission or any other forms of active or developing virus create challenges to transport staff as they attempt to deliver care in a practical and efficient manner. With the large disparity in clinical presentation, means of transmission, effect on exposed personnel, and functional and safety concerns associated with interhospital critical care, identifying a practical means of complete isolation of herpes virus in the realm of medical transport has been difficult. Research-based infection control standards, equipment decontamination, and communication

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