Human Herpesviruses 1 and 2

A Review

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Abstract

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Herpes simplex virus (HSV) is one of the most common infections in the human population. The human herpes simplex viruses include two distinct but closely related viruses designated as HSV-1 and HSV-2. By age 70, about 90% of Americans have become infected with HSV-1. A 30% increase in genital infections with HSV-2 has been reported by the Center for Disease Control.

Although HSV-1 and 2 have been considered site specific, HSV-1 associated with oral lesions and HSV-2 considered a genital infection, the typing of virus isolates has indicated this to be questionable conclusion. An infection with HSV-1 or 2 may have devastating consequences in those who are immunosuppressed due to organ transplantation, cancer chemotherapy, or infected with human immunodeficiency virus. Although the neonatal mortality from HSV has declined with the development of new antiviral medications, the morbidity of neurological complications remains about 50%.
Without the understanding of the disease among clinicians and the continued efforts to ameliorate its effects, HSV will continue to be a devastating diagnosis for most individuals.

The purpose of this article is to provide a review of HSV-1 and 2, and to discuss the pathogenesis, transmission, clinical manifestations, laboratory diagnosis, complications and treatment of this disease.
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INTRODUCTION

Herpes simplex, caused by *herpesvirus hominis* (herpes simplex virus, HSV), is one of the most common human infections with the virus transmissible to any body site (Roisman, et al. 1996) The human herpes simplex viruses include two distinct but closely related viruses designated as HSV-1 and HSV-2. HSV-1 has long been considered an infection of the oral mucosa. More than 135 million Americans over 12 years old are infected with HSV-1 (Center for Disease Control CDC, 1997). By age 70, about 90% of Americans have become infected with HSV-1 (Schillinger, 1998).

A 30% increase in genital infections with HSV-2 has been reported by the Center for Disease Control (CDC, 1997) in the 13 years since the last survey. Although HSV-1 and 2 have been considered site specific, the typing of viral isolates has indicated this to be a questionable conclusion (Lycke, 1991; Puthavathana, 1998; Tayal, 1998; Lipson, 1998). Rates of HSV-1 genital infection vary from 10% to 63%, with the highest percent occurring when testing was done in a sexually transmitted disease (STD) clinic. The changes in sexual practices with the increasing acceptance of oro-genital sex to avoid pregnancy and human immunodeficiency virus (HIV) may have changed the epidemiology of HSV (Wellings, Field, & Wadsworth, 1994; Edwards & Carne, 1998). HSV infections are part of the 15.3 million new cases of sexually transmitted diseases (STDs) that occur in the United States each year, 25% of them among teenagers (Center for Disease Control, 1997).
HSV continues to be as a devastating diagnosis for most individuals, with the most serious pathophysiologic implications being specific to immunocompromised patients and neonates. Although neonatal mortality from HSV disease has declined from 70% to 40% since the development of acyclovir, the morbidity of neurological complications remains about 50% (Whitley, 1991). The number of complications from HSV has increased due to more aggressive cancer chemotherapy regimens, organ transplantation, and increased incidence of human immunodeficiency virus (HIV) infections (Levin, 1993).

There is a wealth of research information about HSV. The purpose of this article is to provide a review of HSV 1 and 2, and to discuss the pathogenesis, transmission, clinical manifestations, laboratory diagnosis, complications, and treatment of this disease.

Viral Description

Human herpes infections have been mentioned in medical literature since the 17th century (Corey, 1994). More than one hundred Herpeviruses, family Herpesviridae, have been isolated with at least one occurring in most animal species. The herpesviruses have been classified into 3 subfamilies. The human herpesviruses (HHV), 8 of which have been identified to date, fall into these subfamilies. Alphaherpesvirinae includes genus Simplex virus, HSV-1 and HSV-2, and genus Varicellovirus, HHV-3 (varicella-zoster virus). Betaherpesvirinae includes HHV-5 (cytomegalovirus, CMV) and HHV-6 (Roseolovirus) with HHV-7 a possible co-factor in Roseola. Gammaherpesvirinae includes HHV-4 (Ebstein-Barr virus) and HHV-8, which is involved in the development of malignancies such as Kaposi’s sarcoma (Roisman, et al, 1996).
HSV-1 and HSV-2 share extensive nucleic acid sequencing and are approximately 50% genetically identical expressing several common antigens (Lycke, 1991). Infection with one type of HSV induces partial immunity against the other (Lycke, 1991). It has been speculated that the two types of HSV originate from a common ancestor, with HSV-1 evolving from HSV-2 (Lycke, 1991).

The virion is composed of linear double-stranded DNA within an icosahedral capsid. The virus’s lipid bilayer is studded with approximately 10 glycoproteins, which are essential for virus penetration into the host cell. The glycoproteins are also targets for the host development of protective antibodies that limit the viremia associated with a primary infection (Dwyer & Cunningham, 1993). Upon host cell entry, the virus replicates in the nucleus and quickly destroys the cell with the resulting development of vesicles on the epidermis. After initial replication in the epithelial cells, the virus enters the sensory nerves and is transported to the sensory ganglia where it either causes acute infection or becomes latent. A lifelong latent infection is established whether or not the primary infection is symptomatic (Vanderhooft & Kirby, 1992). Neuronal cellular events during latency are not well understood. Reactivation of latent infection is related to latency activating transcripts (LATs) in the neuron (Lekstrom-Himes, Pesnicak, & Strauss, 1998). With reactivation, the viral particles travel back down the nerve producing lesions in a highly localized area or produce asymptomatic viral shedding in the absence of lesions (Dwyer & Cunningham, 1993). The skin reactivation theory suggests that various physical disturbances (ultraviolet light, friction, trauma, heat, and cold) trigger viral shedding. Other theories suggest that hormonal and psychological
stress may alter the defense mechanisms resulting in reactivation of the virus (Lycke, 1991).

HSV infection stimulates both a humoral and cell-mediated immune response that differs in primary and recurrent attacks (Dwyer & Cunningham, 1993). In primary episodes, non-specific defense with interferon, natural killer cells and macrophages restrict local viral replication. This is followed by the production of a specific antibody that is important to restrict the spread and limit viremia (Dwyer & Cunningham, 1993). Cell-mediated immune response involving the helper T lymphocyte and cytotoxic T lymphocyte is also important in controlling a primary episode. In recurrent infections, antibody titers have not been correlated with frequency or severity of recurrence. Antibody titers typically do not change in recurrent infection (Corey, 1994). The cell-mediated immune response appears to be much more important than humoral immunity. The major cells infiltrating recurrent herpetic lesions are CD4+ lymphocytes and macrophages. This is confirmed by the severe, chronic and disseminated infections in those with lymphomas, transplantation or AIDS who all have defective cell-mediated immunity when compared to immunocompromised patients with defective humoral immunity (Corey, 1994).

Transmission

Infection with HSV is initiated by direct contact with infected secretions on mucosal surfaces. This may involve spread by virus-containing fluid such as saliva and respiratory droplets. Primarily, infection occurs with mucus membrane contact of the mouth, throat, genital and anal areas. Since the viral envelope is very fragile, fomite or animate transmission is rare. The virus can be inoculated on any body surface. For
example, “herpetic whitlow,” an infection of the finger often seen in dental practice prior to the use of gloves, and atypically the breasts, thighs, buttocks or other areas. Inoculation of the virus onto the conjunctiva causes HSV keratoconjunctivitis and may lead to blindness. Herpes Gladiatorum is defined as HSV infection acquired during the close contact of athletics, such as in wrestling (Habif, 1996).

The continued increase of HSV, both clinical and sub-clinical infections, is of concern because of the implication for the risk of coincident spread of HIV. Evidence suggests that genital and oral ulceration provides a portal of entry during contact with HIV-infected secretions (Stamm, Handsfield, & Rompalo, 1988).

Neonatal infections are acquired perinatally from contact with infected secretions at delivery. Fetal monitor probes have been associated with cutaneous infections of the neonate’s scalp. Although rare, intrauterine infections may occur due to virus transmission across the placenta (Dwyer & Cunningham, 1993). Post-natal infections from hospital personnel and close contacts that have orolabial herpes or herpetic whitlow have been reported (Vanderhooft & Kirby, 1992).

Transmission of HSV occurs primarily from asymptomatic sources. Over 50% of those acquiring genital herpes, get it from partners who do not have symptoms. Asymptomatic infection is relatively common in pregnancy given that 50 to 70% of neonates infected with HSV are born to mothers without history of HSV infection (Whitley, 1995). Perianal shedding of HSV in patients with AIDS is common even among those without a history of perianal lesions (Pannuti, et al, 1997).
Clinical Manifestations

HSV disease includes primary symptomatic and asymptomatic infection, non-primary first episode, and recurrent symptomatic and asymptomatic infection. Infections due to HSV-1 or HSV-2 cannot be distinguished by clinical observation (Dwyer & Cunningham, 1993). Clinical symptoms of mucocutaneous infection progress from vesicle formation, ulceration, to crusting with complete healing without scarring. The differential diagnoses includes syphilis, lymphogranuloma venerum, chancroid, squamous cell carcinoma or HIV in chronic lesions, herpes zoster, contact dermatitis, aphthous ulcers, traumatic ulcers and Behcet’s disease.

Primary infection is infection of an individual who has not previously been exposed to HSV. Primary infections are more severe in pregnant women, neonates and the immunosuppressed, resulting in an increased incidence of herpetic meningitis, encephalitis, hepatitis, and dissemination (Scott, Hollier, & Dias, 1997). Other complications of primary HSV include infections from autoinoculation and super infections with bacteria or fungi (Dwyer & Cunningham, 1993). Asymptomatic primary infections are more common with HSV-1, but may also occur with HSV-2. Primary infection with both HSV-1 and 2 at the same time has been documented in the literature (Miller, Whittington, Coleman, & Nigida, 1987).

A complication of primary infection with HSV-2 is aseptic meningitis. It is the third most common cause of aseptic meningitis. Symptoms include headache, fever, and stiff neck preceded by genital symptoms. Occasionally meningitis is seen in recurrent HSV-2 or HSV-1 infections. Confirmation of infection is evidenced by detection of PCR of HSV DNA in the cerebral spinal fluid in patients with severe symptoms. Aseptic
Meningitis is self-limiting and specific treatment is not required (Dale & Federman, 1997).

*Non-primary first episode or initial infection* is infection of an individual with prior exposure to HSV-1 or HSV-2. Approximately 30 to 60% of those with a first episode of HSV, will have pre-existing antibodies. Usually, this is due to previous oral infections with HSV-1, but 10% to 30% will have HSV-2 antibodies, suggesting previous asymptomatic infection with HSV-2 (Dwyer & Cunningham, 1993). A non-primary infection may or may not present with less severe symptoms than a primary infection (Scott, Hollier, & Dias, 1997).

*Recurrent herpes infection* is the reactivation of a latent virus that results in either symptomatic or asymptomatic infection (viral shedding). Although there is great variability, recurrent infection is shorter and less severe than a primary or non-primary first episode (Dwyer & Cunningham, 1993). Many will experience a prodromal stage during which such symptoms as tingling, itching, burning or other neuralgia will occur. Viral shedding may have already begun by this time.

*Oral-labial Herpes*

Primary HSV infection is often asymptomatic with the greatest exposure occurring in children before the age of 5 through saliva and respiratory spread. Infection may also be acquired by oral sexual contact and may vary from mild pharyngeal erythema to diffuse ulceration that mimics streptococcal pharyngitis (Vanderhoof, 1992). When symptomatic, the infection may be extensive, involving oral lesions, fever, pharyngitis, and cervical adenopathy. More typically, presentation involves painful
vesicles on the vermilion border that form crusted lesions. Incubation time is 2 to 12 days with signs and symptoms persisting up to 21 days (Dale & Federman, 1997).

Recurrent infections seem to be precipitated by exposure to sunlight, wind, local trauma and emotional stress. Oral HSV-1 re-infections develop in 20 to 50% of the population, whereas oral HSV-2 reoccurs at a 5% rate (Landry, Myerson, & Dull, 1992). This may be related to the ability of the two types of HSV to establish latency in either the sacral or trigeminal ganglia and to differences in growth and reproductive patterns (Su, Wu, & Lin, 1995; Lekstrom-Himes, Pesnicak, & Straus, 1998).

*Genital Herpes*

In the case of genital herpes, primary infections are usually extensive and have more systemic symptoms. The incubation period may be anywhere from 3 to 20 days, with complete resolution of symptoms in 6 weeks. In males, infection of the penis is called herpes progenitalis. Generally, HSV infection in the immunocompetent male is less severe than in women. Men are less likely to experience systemic symptoms such as fever, malaise, headache, and lymphadenopathy (Vanderhooft & Kirby, 1992). Symptoms for women may be severe and painful with grouped vesicles on an erythematous base that are in bilateral formation over the labia, perineum, buttock, and thighs. There is cervical involvement in 80% of women experiencing a primary infection. Recent research refutes the previous speculation that cervical HSV is associated with cervical neoplasia (Munoz, et al., 1995). Urethritis is common in both men and women, with more frequent urinary retention in women. Perianal and anal infections in men and women who engage in anal sex may present with pain, tenesmus,
discharge, and sacral paresthesias (Dale & Federman, 1997). Asymptomatic primary infections are more common with HSV-1, but may also occur with HSV-2.

Recurrent genital infections are usually shorter and milder than primary episodes, but still affect women more severely than men. After a prodromal phase of itching, tingling or tenderness, lesions develop on the penis, labia, perineum, mons pubis, or in the perianal region. Symptoms generally resolve in 6 to 10 days. Benign meningitis may be associated with recurrence (Dale & Federman, 1997). Recurrence of HSV-2 in the genital area is estimated to be 6 episodes per year with the greatest likelihood in those with a severe primary infection. HSV-1 recurrences are approximately 1 per year for genital infection (Landry, Myerson, & Dull, 1992).

Asymptomatic viral shedding is three times more frequent in the first 3 months after a primary infection with HSV-2 (Corey, Koelle, Benedetti, & Langenberg, 1992). Asymptomatic viral shedding appears to increase around the time of a symptomatic infection. Patients with HSV-2 should be advised of the high rate of shedding and the potential for transmission to sexual partners. Recent research indicates that suppressive therapy reduces asymptomatic viral shedding by 95% (Wald, Corey & Cone, 1997).

Unfortunately, many healthcare providers still falsely reassure their patients that unprotected intercourse is safe in the absence of identifiable symptoms and fail to offer suppressive chemotherapy.

*Feces Flaccidum*

Diffuse cutaneous dissemination of HSV is a rare complication of the disease that may occur in those who have atopic dermatitis, pemphigus vulgaris, and severe seborrheic dermatitis (Habif, 1996). Infection most often occurs with a primary HSV-1
or HSV-2 infection. The disease is most common in an area of active dermatitis, but normal skin may be involved. The typical vesicular formation appears over a period of 7 to 10 days. The eruptions spread widely and are accompanied by fever, malaise, and adenopathy. The vesicles coalesce to form large erosions, which often become secondarily infected with staphylococcus. Resolution of the untreated infection in uncomplicated cases occurs in 2 to 6 weeks. Recurrent disease is milder and usually without constitutional symptoms (Habif, 1996).

**Ocular Herpes**

In the USA, there are approximately 500,000 cases of ophthalmic HSV infection every year. Infections of the eye with HSV may cause a keratitis, which is one of the most common viral causes of blindness (Dale & Federman, 1997). With keratitis, scleritis, uveitis, or retinitis, vision is lost due to scarring especially with repeated untreated infections. More than 90% of the cases present with unilateral symptoms (Dale & Federman, 1997). Many of these infections begin with conjunctivitis. Characteristic branching dendritic appearance of the lesion may be seen with a fluorescein dye to the cornea. Polymerase chain reaction (PCR) or viral culture of scrapings from the lesions may confirm the diagnosis. Ophthalmic infections most often occur by autoinoculation from oral or genital lesions. This is most common during a primary HSV infection (Corey & Simmons, 1998). Twenty-five to fifty per cent of ocular HSV infections recur within two years (Corey & Simmons, 1997).

**Herpes in the Immunocompromised Host**

Disorders of T cell-mediated immunity are associated with more severe and chronic HSV infections. Herpes infections may have an atypical appearance and are
often large, deep, necrotic, and painful. Bacterial and candida superinfections may further distort the clinical picture. Chronic perianal ulcers caused by HSV have been misdiagnosed as decubitus ulcers (Habif, 1996). Diffuse infections have been identified as impetigo. If untreated, lesions in the severely immunocompromised patient persist until reversal of the immune suppression following transplantation or antiviral therapy is provided. Asymptomatic viral shedding may be prolonged in the absence of active lesions with both transplantation and AIDS (Habif, 1996; Panmuti et al., 1997).

Viral encephalitis is almost always seen in the immunocompromised host or the neonate. HSV-1 presents with more focal disease of the frontal lobe with fever, lethargy, and headache. Confusion and focal seizures occur in approximately 40% of immunocompromised patients. If the dominant lobe is involved, aphasia and focal motor and sensory deficits develop. In an infection with HSV-2, more diffuse symptoms are evident. AIDS predisposes a person to HSV encephalitis and often occurs in conjunction with other central nervous system (CNS) infections such as CMV. Cerebral edema is the most frequent cause of death due to HSV encephalitis. Indefinite prophylaxis with antiviral therapy may be required to suppress the virus and further symptoms (Dale & Federman, 1997).

*Herpes in the Neonate*

Prevalence of HSV infection in neonates is estimated to be 1 in 2500 and includes mucocutaneous infection, CNS infection, and disseminated disease (Corey & Simmons, 1997). The risk of infection to the neonate depends on the type of maternal infection and the route of delivery. If the neonate is delivered vaginally in the presence of a first episode lesion (primary or non-primary), the risk of infection is around 50%. If the first
maternal HSV episode is asymptomatic, the neonatal risk drops to 33% (Scott, Hollier, & Dias, 1997). The exposure of the neonate to a recurrent symptomatic infection with a vaginal delivery reduces the risk of transmission to around 4%. In the absence of vaginal lesions and symptoms in a mother with known HSV, the risk of neonatal transmission is about .04% (Scott, Hollier, & Dias, 1997).

An HSV infection of the skin, eyes and mucus membranes is evident in 45% of neonatal herpes and has the best prognosis. The onset of infection may be evident at birth, but mean time to diagnosis is about twelve days (Habit, 1996). With early recognition and treatment, approximately 2% will progress to the CNS or a disseminated infection (Scott, Hollier, & Dias, 1997), although the presence of more than 3 reoccurrences in the first year is associated with more neurological impairment (Habit, 1996).

Disease that is limited to the CNS occurs in approximately 35% of infected neonates. The presenting symptoms include fever, lethargy, and seizures. Vesicles are present about 50% of the time. The mortality rate with treatment is approximately 15%, but morbidity occurs with such serious sequelae as hydrocephalus, encephalic cysts, psychomotor retardation, and blindness (Dwyer & Cunningham, 1993; Habit, 1996). HSV-2 encephalitis tends to be more severe than HSV-1 with a greater frequency of residual seizure and brain damage (Scott, Hollier, & Dias, 1997; Dwyer & Cunningham, 1993).

The least common form of infection, disseminated HSV, occurs in approximately 20% of infected neonates. The initial symptoms are nonspecific and vesicular lesions are usually absent, initially (Dwyer & Cunningham, 1993). The infection often involves
the liver, lung, brain, adrenals, and skin. Mortality is about 57%, with HSV pneumonitis being the primary cause of death. Severe and varied neurological deficits are present in 41% of survivors (Habif, 1996).

Prevention of neonatal herpes is a challenge when most cases are associated with maternal asymptomatic viral shedding and an absence of a history of genital herpes (Habif, 1996). Even in the absence of signs or symptoms of maternal HSV infection, neonatal herpes infection should be at the top of the differential diagnosis list whenever an infant has nonspecific or neurologic findings (Scott, Hollier, & Dias, 1997). If obvious skin lesions are not available to culture initially, the next diagnostic evaluation in a symptomatic neonate is a lumbar puncture with polymerase chain reaction (PCR) testing of spinal fluid (Tilton, Ballows, Hohnadel, & Reiss, 1994). With a high index of suspicion and early initiation of antiviral treatment, the minimum neurologic consequences may be evidenced.

**Herpes in Pregnancy**

Genital HSV in pregnant women generally follows a typical benign, self-limiting course as seen in the nonpregnant woman. However, primary infections in pregnancy may be more severe in some cases, resulting in herpetic meningitis, hepatitis, or disseminated infection (Scott, Hollier, & Dias, 1997). In addition, primary HSV in late second and third trimester is associated with preterm labor, intrauterine growth retardation, and transplacental infection of the fetus. Primary infection in the first trimester may induce spontaneous abortion, but fetal defects have not been documented (Dwyer & Cunningham, 1993).
In the effort to reduce neonatal infections, the management of HSV in late pregnancy has led to significant maternal risks. During the 1970’s and 80’s, it was estimated that 4 mothers died from complications of cesarean section for every 7 babies saved from herpes-related deaths (Randolph, Washington, & Prober, 1993). With a change in the guidelines by the American College of Obstetricians and Gynecologists (ACOG, 1988), the cesarean delivery rate has decreased from 50% to 17% without an increase in neonatal herpes infection (Roberts, Cox, & Dax, 1995). The current recommendations by ACOG are as follows: the patient is to be examined when she presents for delivery. If she has an identifiable genital lesion or describes prodromal symptoms, she is to be delivered abdominally, regardless of how long her membranes have been ruptured. If there are no visible lesions and no prodromal symptoms, a vaginal delivery is indicated.

Herpes Implicated in Other Infections

HSV infection precedes up to 75% of cases of erythema multiforme, a mild to severe rash illness with urticarial papules and target lesions (Habif, 1996). Recurrences are suppressed with acyclovir treatment. Viral reactivation in the temporal ganglia is the suspected cause of Bell’s palsy, a paralysis or weakness of the muscles supplied by the facial nerve (Schulz, et al., 1998). Inoculation disease due to HSV has been implicated in unusual skin lesions in the immunocompromised including a case report that described an infection in the great toe. The diagnosis was delayed despite the presence of typical lesions resulting in inappropriate treatment and prolonged discomfort (Weaver & Kostman, 1996).
Laboratory Diagnosis

The diagnosis of genital HSV-1 or 2 has the potential for significant physical and psychological impact on an individual. In the neonate, it is essential to have a quick, accurate identification of vesicular lesions. The type of test ordered to confirm a diagnosis may change under varying circumstances, but testing generally should be offered in any situation in which HSV is suspected. Unfortunately, a herpes lesion may be seen as a small fissure or a raw area. The healthcare provider must have a high index of suspicion to increase the sensitivity of diagnosis.

Viral cultures represent the “gold standard” for the diagnosis of HSV infection (Vanderhoof & Kirby, 1992). Typically, a specimen is inoculated onto a tissue cell culture followed by daily microscopic observation for cellular changes. Approximately 50% of infected specimens will be positive within 24 hours and the rest within 5 to 7 days (Tilton, Ballows, Hohnadel, & Reiss, 1994). Once the virus has been isolated, it can be typed as HSV-1 or HSV-2 by the use of monoclonal antibodies. The virus can be isolated in up to 90% of vesicles and pustules, compared with 30% or less from crusted lesions (Baron, Peterson, & Finegold, 1994). Ideally, cultures should be obtained from the newest lesion, typically formed within 7 days of onset for first-episode lesions and within two days for recurrent lesions (Tilton, Ballows, Hohnadel, & Reiss, 1994). Due to the possibility of false negative cultures, the individual must be counseled that a negative culture does not rule out herpes infection and cultures of future lesions may be necessary to establish the diagnosis (See Table 1).

The detection of HSV by PCR is highly sensitive and specific (Slomka, Emery, Munday, Mousdale, & Brown, 1998). In a number of studies, PCR assays were found to
be more sensitive than cell culture (Hobson et al., 1997; Lucotte et al., 1995). The test will likely take the place of cell culture as the "gold standard" for detection and typing of HSV. In the presence of lesions, PCR DNA can detect HSV longer in the course of an infection than the viral culture collection. It is also more sensitive for detecting asymptomatic viral shedding (Corey, 1994). The specimen collection is the same as with the cell culture method, using the appropriate Dacron or Rayon swab and viral media (Filton, Ballows, Hohnadel, & Reiss, 1994). PCR testing may be especially valuable for the early detection of HSV DNA in cerebral spinal fluid (CSF) in cases of suspected encephalitis (PAML, 1999).

Cytology stains for the initial diagnosis of HSV have long been used. Changes in cell features can be detected by microscopy with such stains as Papanicolaou's, Giemsia, or Tzanck. The stained sample from a lesion will have the characteristic multinucleated giant cells (Baron, Peterson, & Finegold, 1994). The specificity of these cytology methods approaches 95%, but the sensitivity is only about 50%. Recovery of the specimen from a recently formed vesicle rather than a crusted lesion improves the sensitivity, as with the cell culture method (Baron, Peterson, & Finegold, 1994).

With the emerging awareness that herpes infection is largely an asymptomatic disease and that transmission often occurs during periods of asymptomatic viral shedding, accurate serologic testing is becoming increasingly important (Pereira, 1996). The traditional serologic test does not reliably differentiate between the two serotypes and is not truly useful in diagnosing or screening for genital HSV. The presence of antibody (IgM and IgG) from an infection with one type of HSV makes the serologic diagnosis of the other type difficult. The serological testing can document seroconversion with an
acute and convalescent serum sample taken at the time of suspicious symptoms and 2 to 3 weeks later (Baron, Peterson, & Finegold, 1994). New serological tests that identify a specific glycoprotein G on the virus surface have provided a type-specific method to distinguish HSV-1 from HSV-2. The CDC recommends, that if serological testing is to be used, these new type-specific tests should replace the traditional IgM and IgG tests (Handsfield, Stone, & Graber, 1998).

Detection of HSV antigens can be used with rapid tests such as immunofluorescence (IF), immunoperoxidase (IP), and enzyme immunoassay (EIA). These results can be made available in 1 to 6 hours after specimen collection from a lesion. As with most sample collections, these tests show a higher sensitivity when the lesions are vesicular (Baron, Peterson, & Finegold, 1994). See Table 1 for a review of the diagnostic tests.

Treatment

Therapeutic goals in the treatment of HSV are to relieve discomfort, promote healing, prevent complications, and decrease the duration of viral shedding. Important intervention strategies also include education, counseling and emotional support. According to a study done in 1991 by the American Social Health Association (ASHA), most patients with a diagnosis of HSV had tried 2 to 5 therapies including over-the-counter remedies, herbals, vitamins, nutritional changes, and multiple unproven “cures” after the initial diagnosis by a health care provider. The use of L-lysine, an amino acid, in the amount of 200 to 1000 mg a day has been anecdotally effective but has not yet been supported by research (Milman, N, 1980; Griffith, R.S, 1978).
The development of antiviral drugs (nucleoside analogues) over the past 15 years has been the most important advance in the treatment of HSV (Whitley, 1996). These drugs disrupt the viral replication by interfering with DNA synthesis in the HSV infected cell. Activation of the virus-specific enzyme thymidine kinase (TK) by the host cell further enhances the drug entry into the infected cell (Cassady & Whitley, 1997).

Acyclovir used orally for primary HSV decreases the duration of viral excretion, the formation of new lesions, and the duration of vesicle formation (Habif, 1996). The most common side effects of the medication in short-term use are nausea, vomiting and headache in 2.7% of users (PDR, 1997). Given intravenously (IV), the medication may crystallize in the renal tubules, if the patient is inadequately hydrated (PDR, 1997). The drug is metabolized by the kidney and dose adjustment is indicated for those with acute or chronic renal impairment (PDR, 1997). The safety of systemic acyclovir therapy has not been established in pregnancy, but retrospective review of maternal use has not been associated with neonatal anomalies (Dwyer & Cunningham, 1993). Women who require acyclovir or valacyclovir for disseminated disease in pregnancy may be registered at 1-800-722-9292 ext. 38465 (CDC STD Treatment Guidelines, 1998).

Resistance to acyclovir has developed due to the ability of the viral TK gene in HSV to mutate (Cassady & Whitley, 1997). The resistance to infection with HSV is more likely to develop in immunocompromised patients receiving multiple courses of antiviral treatment (Gaudreau, Hill, Balfour, Erice, & Boivin, 1998). In addition, acyclovir has low and variable bioavailability (Whitley, 1996). Consequently, alternative therapies have been developed. Valacyclovir is a prodrug of acyclovir, has good oral availability with higher serum levels than comparable doses of acyclovir (Cassady &
Whitley, 1997). Patients primarily report vomiting, other gastrointestinal (GI) upsets and headache. Longer-term use in high doses is associated with worsening GI effects, idiopathic thrombocytopena purpura, hemolytic uremic syndrome, and thrombotic thrombocytopenia in some AIDS clinical trials. The renal toxicity and neurotoxicity were less than that of acyclovir in higher doses. Valacyclovir has been as efficacious as acyclovir for HSV treatment and has more convenient dosing due to the longer half-life (Cassady & Whitley, 1997). The oral absorption of the drug is more efficient than IV dosing in conversion to the active form of acyclovir and therefore only an oral form is available (PDR, 1997). Unfortunately, an acyclovir-resistant infection is also resistant to valacyclovir (Cassady & Whitley, 1997).

Famciclovir is another nucleoside analog that is a prodrug of penciclovir. Approximately 80% of the drug is absorbed with oral dosing. Its longer half-life also permits less frequent dosing, than with acyclovir. Headache, nausea and diarrhea occurred in more than 3% (PDR, 1997). In animal studies with rats, mice, and dogs testicular toxicity was observed related to the dose and duration of exposure to famciclovir (PDR, 1997). These findings have not been replicated in humans (Abramowicz & Rizack, 1997). As with acyclovir and valacyclovir, the response to alterations in TK renders famciclovir ineffective in the treatment of resistant HSV.

With the emergence of resistant HSV in the immunocompromised, the typical treatments have also included foscarnet, ganciclovir and vidarabine. These drugs have multiple toxic side effects leading to a continued effort to acquire new treatment. Several new nucleoside analogues are currently in clinical trials. Sorivudine, lobucavir, and cidofovir have promising profiles (Cassady & Whitley, 1997). Many of the newer
approaches to treatment target a specific process unique to HSV and have the potential for highly efficient selectivity. Immunotherapies such as viral vaccines have promising research data (Spector et al., 1998).

Topical treatments for both skin and ophthalmic infections are available. A topical penciclovir has been marketed for the treatment of recurrent orolabial HSV. Applied every two hours while awake for 4 days led to reduced pain and increased healing time by approximately one day. Topical treatment with acyclovir is substantially less effective than systemic treatment and its use is discouraged (CDC, 1998).

Trifluridine and topical cidofovir 1% gel are ophthalmic preparations for use against acyclovir resistant HSV (Abramowicz & Rizack, 1997). Antiviral medications partially control signs and symptoms when used as daily suppression therapy in selected populations (symptomatic episodes > 6 per year). The suppressive therapy ameliorates or even prevents recurrence more than 75% of those infected with HSV (CDC, 1998). The safety of oral acyclovir is established with up to 6 years of continuous use. Suppression with valacyclovir and famciclovir are considered safe for up to one year. The long-term use of these medications has not been implicated in the development of resistance in the immunocompetent (CDC, 1998). In the immunocompromised, suppression of HSV with continuous therapy also reduces the recurrence and subclinical shedding of the virus, but often requires larger doses with attendant side effects and the development of resistance (CDC, 1998).

Table 2 provides the CDC 1998 treatment recommendations for selected HSV infections.
<table>
<thead>
<tr>
<th>Type of infection</th>
<th>Treatment *</th>
<th>Costs **</th>
</tr>
</thead>
</table>
| Oralabial HSV     | Acyclovir 400mg PO tid x 7 to 10 days  
|                   | Penciclovir 1% cream q2h while awake  | 34.14  
|                   |                                         | 30.57 |
| First episode     | Acyclovir 400mg PO tid x 7 to 10 days  
| Recurrence        | or                                        | 34.14  
|                   | Famiclovir 250mg PO tid x 7 to 10 days   | 45.95  
|                   | or                                        | 46.37  
|                   | Valacyclovir 1 gm PO tid x 7 to 10 days  |          |
| First episode     | Acyclovir 400mg PO tid x 5 days          | 28.33  |
| Recurrence        | or                                        | 25.71  |
|                   | Acyclovir 800 mg PO bid x 5 days         |          |
|                   | or                                        |          |
|                   | Famiclovir 125mg PO bid x 5 days         | 24.52  |
|                   | or                                        | 27.60  |
|                   | Valacyclovir 500mg PO bid x 5 days       |          |
| Suppressive therapy | Acyclovir 400mg PO bid x 1 year         | 113.32 |
|                   | or                                        |          |
|                   | Famiclovir 250mg PO bid x 1 year         | 183.80 |
|                   | or                                        |          |
|                   | Valacyclovir 500mg PO bid x 5 days       | 165.60 |
| Ocular HSV        | Trifluoridine 1 gtt solution q2h up to 9gtt for 10 days | 53.13  |
| Neonatal HSV      | Acyclovir 500mg/m2 IV for 10 to 21 days  | 126.02 |
| Mucocutaneous     |                                           |          |
| Encephalitis      |                                           |          |
| Disseminated      |                                           |          |
| Herpes simplex    | Acyclovir 10mg/kg/IV q8h until resolution | Price varies by  
| Infants           | Oral supension: 25 to 30mg/kg/day        | weight    |
| Children          |                                           |          |
| Pregnancy HSV     | Acyclovir 400 mg PO tid x 7 to 10 days  | 34.10  
| Primary if severe | Acyclovir 10 mg/kg IV q8h x 10 days      | 3718.91 |
| Encephalitis      |                                           |          |
| Acyclovir resistant HSV | Foscarnet 40mg/kg/q8h IV x 14 to 21 days | 1459.25 |


** Abramowitz and Rizack, 1997. Drugs for non-HIV infections.
Counseling: HSV infections

The psychosocial implications of HSV in nongenital infections have been believed to have little social stigma attached to the diagnosis and few studies have been published about general knowledge or psychological implications. Genital HSV, on the other hand, is known to cause profound effects on the lives of those diagnosed with the infection according to numerous studies (Woolley & Kinghorn, 1986; Bierman, et al, 1985). Those interviewed regarding their diagnosis describe symptomology with feelings of anger, feelings of shame, and lowered self-esteem. Often discussed are the concerns around the absence of cure, the recurrent nature of the symptoms and the fears of transmission in pregnancy or to a future partner (Corant, et al, 1996).

In the study conducted by the ASHA, over 60% of the respondents felt that the health care community responded to those with a new diagnosis of HSV inadequately in the areas of social support and information. Many health care providers were uncomfortable or lacked time for psychological support or sexual counseling (Catotti, Clark, & Catoe, 1993). Counseling should focus on educating patients and increasing coping and acceptance abilities (Longo & Koehn, 1993). The specific points to be made are as follows.

1. HSV can be transmitted in the symptomatic and asymptomatic stages of infection with the greatest risk during the symptomatic stage.

2. It is likely that the risk of HSV may be reduced by the regular and consistent use of condoms, but condoms do not completely eliminate the risk of transmission.
3. The severity and duration of clinical recurrence is less with the use of suppressive antiviral chemotherapy.

4. Oral sex is a route for the transmission of the virus as is non-sexual contact.

5. Routine prenatal screening for a woman and her partner may have a future role in the prevention of neonatal HSV infections.

6. Resources are available for information and support (especially the Internet). These resources should be made available.

Summary

Herpes infections continue to increase in the United States. HSV-1 infections are largely asymptomatic infections of childhood and confer a partial immune response when exposure occurs to HSV-2. Large numbers of unrecognized individuals with symptomatic and asymptomatic shedding are the likely source of the continued genital HSV-2 increase. Recent studies that indicate a potential for the antiviral agents to reduce HSV shedding may be useful in preventing some aspects of transmission. The advances in laboratory techniques may assist in the diagnosis of asymptomatic disease in high-risk individuals. The connection between HSV and HIV continues to be strengthened in the research, but the question remains unanswered whether reducing the HSV impact on HIV positive patients will produce a reduction in the viral load of HIV.

Recommendations to Nursing

If the health care community becomes more aware of the epidemiology, diagnosis and treatment of this disease, then the impact of HSV on the individual, with its
physical and emotional consequences, can be attenuated. Educational efforts should be focused in the primary care setting to enhance recognition of the disease. More education of all health care providers to the emotional impact of this disease may provide the necessary tools to offer adequate support and appropriate referral for additional intervention.
<table>
<thead>
<tr>
<th>Technique</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Cost</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virus-cell culture</td>
<td>80-100%</td>
<td>100%</td>
<td>$85.40 + 42.05 to type: 1 or 2*</td>
<td>2-7 days</td>
</tr>
<tr>
<td>Antigen: IF, IP</td>
<td>55-80%</td>
<td>90%</td>
<td>$137.60</td>
<td>1-2 hours</td>
</tr>
<tr>
<td>FIA</td>
<td>70-93%</td>
<td>95%</td>
<td>$69.08</td>
<td>4-6 hours</td>
</tr>
<tr>
<td>Virus-PCR</td>
<td>100%</td>
<td>100%</td>
<td>$170.00*</td>
<td>3-5 days</td>
</tr>
<tr>
<td>Serology IgM IgG by ELISA</td>
<td>95-99%</td>
<td>99-100%</td>
<td>$353.98*</td>
<td>1-3 days</td>
</tr>
<tr>
<td>gG1 and gG2</td>
<td>98-99%</td>
<td>99-100%</td>
<td>$179.20</td>
<td>1-3 days</td>
</tr>
<tr>
<td>Cytology Tzanck</td>
<td>50%</td>
<td>95%</td>
<td>$ 10.00*</td>
<td>&lt; hour</td>
</tr>
</tbody>
</table>

*Pathology Associates Medical Laboratory (PAML), Spokane, WA: Prices Dec. 1998

ARUP Laboratories, Salt Lake City, Utah: Prices Mar. 1999. 1-800-522-2787

Definition of Abbreviations: IF-immunofluorescence, IP-immunoperoxidase, EIA-enzyme immunoassay, PCR-polymerase chain reaction, IgG-immune globulin G, IgM-immune globulin M, and ELISA-enzyme linked immunoassay.
References


Pathology Associates Medical Laboratory (PAML). (1998). P.O. Box 2687 Spokane, WA 99220.


