Herpes simplex virus (HSV) is a devastating infection in the neonatal patient. The incidence of maternal HSV infection and consequent neonatal infection has increased significantly over the last several decades due to changing sexual practices. Despite the improvements in outcome with the use of high dose acyclovir, a delay in the diagnosis of HSV has been associated with progression of the disease and increased mortality and morbidity. Even with adequate treatment, permanent sequelae, such as developmental delay, cerebral palsy, blindness, and persistent seizures may occur. Since the onset of symptoms can occur up to four weeks of age, clinicians caring for infants in any setting including the neonatal intensive care unit, the well baby nursery, pediatric floors, emergency rooms, and outpatient clinics must be fully aware of the clinical presentation, evaluation, treatment, and prevention of neonatal HSV infection to facilitate successful diagnosis and treatment of this deadly disease.

Since the 1970s, the medical community has seen a dramatic increase in the incidence of herpes simplex virus (HSV) infection in the general population.[1,2] This surge in the prevalence of herpes infection in women of childbearing years has unfortunately led to a comparable increase in the incidence of neonatal herpes infection.

Herpes infection in the newborn is often a devastating disease associated with an extremely high mortality and morbidity.[1] Although tremendous advances in the provision of care to the neonatal patient have been made, the incidence of neonatal herpes has continued to increase.[1,2] Herpes infection in the newborn is extremely virulent; even aggressive therapy may be only minimally successful. Delay in both the diagnosis and treatment of neonatal herpes infection has been associated with rapid progression of the disease process and a dramatic increase in both the mortality and morbidity.[3] Therefore, clinicians caring for infants in any setting including the neonatal intensive care unit (NICU), the well baby nursery, pediatric floors, emergency rooms, and outpatient clinics must be fully aware of the clinical presentation, evaluation, treatment, and prevention of neonatal HSV infection to successfully diagnose and treat this deadly disease.

Herpes infections have been referenced in medical literature for centuries. Ancient Greeks and Romans coined the term "herpes" meaning to creep or crawl.[4] In the 1700s a French physician, Astru, made the association between herpetic lesions and genital ulcers, but the distinction between the epidemiology and clinical differences of HSV-1 and HSV-2 were not apparent until the 1960s.[5]

HSV is a double-stranded DNA-enveloped virus belonging to the Herpesviridae family, which is further divided into alpha, beta, and gamma. HSV-1 and HSV-2 both belong to the alpha-herpesvirinae subfamily, genus Simplexvirus.[6] Viruses of the genus Simplexvirus are characterized by a variable host range, short replication cycle, and the ability to destroy infected cells and establish latent infections.[6] The basic structure of HSV consists of a central core and an inner core. The central core is comprised of viral DNA surrounded by a coating composed of tubular proteins. An envelope derived from cellular membranes containing viral proteins surrounds the inner core. Embedded in this layer are several viral-encoded glycoproteins (gB, gC, gD, and gE) that are important for attachment to the host cell receptors, cell penetration, and viral immune escape mechanisms.[7]

Herpes virus infection can affect a wide range of cells including both neural and epithelial tissues.[8] Neural tissue infections result in either latency or destruction of neurons and glial cells. Epithelial infection causes destruction of epithelial cells with the formation of a vesicle, which contains a high titer of virus. After primary infection in the epithelial cells, the virus enters the sensory neurons and is transported to sensory ganglia, where it becomes latent and lies dormant. Viral reactivation can occur after stimuli [such as ultraviolet (UV) light, fever, or trauma], facilitating asymptomatic shedding or epithelial infection usually of a less severe nature. Herpes viruses are unique in that they
can establish latency following symptomatic or asymptomatic primary infection and subsequent reactivation can occur with or without symptoms despite the presence of humoral and cellular immunity.\cite{9,10} Thus, an individual infected with HSV is always a potential reservoir of infectious virus.\cite{11}

Genital HSV infections are among the most common sexually transmitted infections in the United States, with 600,000 new cases diagnosed each year.\cite{1,6} Although HSV-2 is the most common cause of genital HSV infections, changes in sexual practices have increased the incidence of genital HSV-1 infections. Epidemiologic studies of HSV show humans are the primary hosts and close interpersonal contact is required for transmission. Factors most highly associated with infection are race, age, and years of sexual experience.\cite{6,12} Several studies showed seroconversion during pregnancy to be about 2 to 3% and often the women are not aware of this conversion as their partners were asymptomatic.\cite{13} Even women in long-term monogamous relationships can become infected because they may not convert for years.\cite{14}

Genital HSV infection in the adult population is classified into three clinical designations, primary genital HSV, nonprimary first episode genital HSV, and recurrent genital HSV. Primary genital HSV is defined as acquiring HSV when antibodies to HSV-1 and HSV-2 are absent. This usually presents with painful vesicles in clusters on the inflammed area. Primary genital HSV may be accompanied by pruritis, dysuria, vaginal discharge, and tender adenopathy. In addition the individual may have fever, malaise, and myalgia for one to two days before lesions appear. Viral shedding begins two days after onset and continues until reepithelialization of lesions. Nonprimary first episode genital HSV is defined as acquisition of HSV-1 or -2 with antibodies to the other type, whereas recurrent genital HSV is reactivation of genital HSV where the lesion is the same type as the sera.\cite{6}

Primary HSV infection in the last trimester of pregnancy carries a transmission rate of 30 to 50% whereas in recurrent infection the transmission rate is decreased to 0 to 5%.\cite{13,15,16} This lower transmission rate is due to the lower viral titer, transplacentally protective antibodies, and lower frequency of cervical viral shedding during recurrent infection.\cite{17}

Neonatal HSV can be acquired intrauterine, intrapartum, or postpartum. It is most commonly caused by HSV-2, but 15 to 30% of cases can be attributed to HSV-1.\cite{18-20} Transplacentally acquired infection accounts for 5% of neonatal HSV infections and is defined as presence of skin vesicles or scarring, chorioretinitis, hydroencephaly, microphthalmia, microcephaly, or an abnormal computerized tomogram (CT) scan of the head within the first week of life.\cite{21,22} These infants frequently present with low birth weight due to prematurity or intrauterine growth restriction and may be extremely ill immediately following delivery with multiorgan system involvement.

Transmission during delivery is the most common route of infection accounting for 86 to 90% of neonatal HSV cases.\cite{6,23} Transmission can be 10 times higher in women who acquire primary HSV late in pregnancy as opposed to recurrent disease.\cite{19,24-26} Predictors of transmission include location, number, and duration of lesions. Cervical shedding as opposed to vulvar shedding and multiple lesions that last longer all increase risk of infection. Unfortunately, identifying who is at risk is difficult, as 60 to 80% of mothers with infected newborns are asymptomatic at delivery and have no history of HSV.\cite{27,28}

Due to the increasing incidence of neonatal herpes infection and the exceptionally high mortality and morbidity of this disease, a high index of suspicion is imperative in all clinicians caring for neonatal patients. Because the clinical symptoms associated with neonatal herpes infection are often nonspecific, they may go unrecognized or may be attributed to another disease process, such as bacterial sepsis.\cite{29,30} Such a delay in diagnosis dramatically increases the mortality and morbidity of infected infants, and therefore all clinicians caring for neonatal patients must be fully aware of the signs and symptoms consistent with neonatal herpes infection as well as the often subtle differences between the clinical presentation of bacterial and herpetic infection.\cite{30}

Neonatal HSV infection can be divided into three clinical groups. Skin, Eyes and Mouth disease (SEM) is a localized infection affecting the skin, eyes, or mouth. Central nervous system (CNS) disease is defined as encephalitis with or without SEM disease. Disseminated disease involves infection in multiple organ systems and can include hepatitis,
pneumonitis, and disseminated intravascular coagulation (DIC).\cite{2,6,31} Cutaneous lesions may be seen in all types and disseminated disease may occur with or without the presence of CNS disease. This classification system is predictive of both morbidity and mortality \cite{32,33}.

Table 1. Comparison Between Types of HSV Infection

<table>
<thead>
<tr>
<th>Type of Disease</th>
<th>Characteristics</th>
<th>Mortality Pretiviral Treatment (%)</th>
<th>Mortality with High Dose Acyclovir (%)</th>
<th>Morbidity Normal Development at 24 Months (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEM</td>
<td>Vesicles on skin, in mouth or eyes</td>
<td>33</td>
<td>0</td>
<td>98</td>
</tr>
<tr>
<td>CNS</td>
<td>± Vesicles meningitis, seizures, encephalitis, lethargy, bulging fontanel</td>
<td>50</td>
<td>4</td>
<td>30</td>
</tr>
<tr>
<td>Disseminated</td>
<td>± vesicles ± CNS disease multiorgan (hepatitis, chorioretinitis, pneumonitis, DIC)</td>
<td>85</td>
<td>31</td>
<td>75</td>
</tr>
</tbody>
</table>

Kimberlin et al.\cite{2} and Kimberlin\cite{3}.

The incubation period for neonatal herpes infection is 4 to 21 days after delivery. Infants typically begin to exhibit signs sometime between 6 and 21 days, with 30 to 40% of infants becoming symptomatic within the first week of life.\cite{2,6,11} Signs are often consistent with those of bacterial sepsis and include fever, temperature instability, lethargy, poor feeding, respiratory distress, and cyanosis.\cite{30,34} As the infection progresses, one may see DIC, hepatitis, pneumonitis, and seizures.\cite{11,29,35} Since these signs may be initially mistaken for those associated with bacterial infection, treatment is often delayed until progression of the disease process occurs, leading to a dramatic increase in mortality and morbidity.\cite{30}

The presentation of neonatal herpes infection differs according to the type of infection. Vesicular skin lesions are the most predominant symptom consistent with neonatal herpes infection and, when lesions are present, herpes infection must be presumed until proven otherwise. These lesions begin as papules, which develop over a few days into ulcers.\cite{29} They are typically thin walled with an erythematous base, are 1 to 3 mm in diameter, and occur either as a single unit or in clusters (Fig 1).\cite{11} Vesicles may appear anywhere on the body but are most commonly seen on the presenting part, such as the head in a vertex presentation or the buttocks in a breech presentation.\cite{30,36,37} They may also present on the face, the soles of the feet, the palms of the hand, and in the mouth. Scalp monitoring sites are notorious for becoming the primary site of infection. These sites must be meticulously examined and a culture taken if evidence of infection exists. If this culture result shows the absence of bacteria, the presence of a herpes infection must be considered.\cite{29,37}
Although vesicular lesions are the most frequent presentation, the absence of lesions should not preclude the consideration of neonatal HSV infection. If the diagnostic focus is centered on the observation of these lesions, many cases of neonatal herpes infection will not be promptly diagnosed. In fact, only approximately 68% of neonatal herpes infection will present with lesions and 17 to 39% of infants with confirmed herpes infection will never exhibit evidence of lesions during their illness. Therefore, the astute clinician must be cognizant of the more subtle presentation of neonatal herpes infection.

Those infants with SEM disease are the most easily diagnosed since they usually present with obvious vesicular lesions. However 17% of infants with SEM disease never exhibit skin lesions. In these cases, the disease is limited to either the mouth or eyes and thus may be difficult to appreciate. Conjunctivitis, especially keratoconjunctivitis, is a classic finding consistent with herpes infection and must be carefully evaluated and appropriately treated. Vesicles in the mouth may be difficult to appreciate especially in the intubated infant and thus a careful examination is warranted. Early diagnosis of SEM disease is imperative since early treatment is associated with a remarkably favorable prognosis. However, if SEM disease is left untreated, 70% of these infants will progress to either Central Nervous System (CNS) or disseminated disease, both of which are associated with an extremely poor outcome.

Infants with CNS disease present with acute symptoms of meningitis, including a bulging fontanel, irritability, abnormal movements or positioning, and most commonly seizure activity. Generalized or localized seizures are the most common symptom associated with herpes meningitis and the diagnosis of herpes infection must be entertained in any infant presenting with seizures with no underlying etiology.

Finally, infants presenting with disseminated herpes disease typically present with symptoms very similar to those associated with bacterial infection. Although the diagnosis may be easily confused, disseminated herpes disease may often be distinguishable from bacterial infection by the presence of vesicular lesions, neonatal hepatitis of unknown etiology, and DIC. Disseminated herpes infection may have a component of CNS involvement and the infant may therefore exhibit symptoms consistent with encephalitis or meningitis.

Although infants with a positive maternal history of herpes infection are often considered at risk for the development of
neonatal herpes infection, these infants actually carry the lowest risk of infection. It is the infant who on first assessment appears to be without risk factors who is in the most danger of infection and in whom the diagnosis is often not promptly recognized. Since the most serious neonatal infections are due to a primary infection in the mother and 60 to 80% of those primary infections are asymptomatic, there may be no history of maternal herpes infection. Therefore, the presence of a negative maternal and/or paternal history cannot reduce the level of suspicion related to neonatal herpes infection.

The clinical presentation of neonatal herpes may be very nonspecific, therefore a high index of suspicion must be present to reduce the mortality and morbidity associated with a delay in diagnosis. However, it is not feasible to initiate acyclovir as a routine therapy in the treatment of all newborns undergoing evaluation for sepsis. Certain situations must be identified in which the likelihood of HSV infection is increased. These situations may include infants with culture negative sepsis, infants with clinical evidence of sepsis that is not responding as expected to antibiotic therapy, and infants with culture negative pneumonia that continues to progress despite treatment with antibiotics. Seizures are also an important manifestation of herpes meningitis and the presence of generalized or focal seizures without evidence of a clear etiology must be considered herpes infection unless proven otherwise.

Not only is neonatal herpes infection of concern for those clinicians caring for infants in the newborn nursery or neonatal intensive care unit, those infants who are considered well newborns and have been discharged home are also at risk of infection. Since neonatal herpes infection can be seen up until four weeks of age, clinicians caring for newborns in clinics, offices, and emergency rooms must be familiar with the clinical manifestations of this disease process. To illustrate the importance of knowledge and education related to neonatal herpes infection, it has been reported that, while parents are noting a change in their infant's condition and promptly bringing their infected infant to the attention of medical personnel, there is then a six- to seven-day delay on the part of the clinician in initiation of proper antiviral therapy, resulting in progression of the disease process.

Any delay in the diagnosis of neonatal HSV infection can have disastrous consequences. While the presence of SEM infection is associated with a 0% mortality rate, without prompt treatment, up to 70% of infants with SEM disease will progress to either CNS or disseminated disease both of which have an increased risk of death or permanent sequelae. Thus clinicians working in both the hospital setting and the outpatient arena must be acutely aware of the clinical manifestations of this disease and regard symptomatic infants with a high degree of suspicion.

As with any clinical entity, the diagnostic procedure must begin with a thorough physical assessment. Findings of vesicular lesions, respiratory distress, hepatosplenomegaly, and/or CNS dysfunction may be indicative of herpes infection. Once a suspicion of a herpes infection arises, a full investigation for the presence of the virus and treatment with antiviral therapy is indicated.

Table 2. Diagnosis of HSV Infection in the Newborn

<table>
<thead>
<tr>
<th>Procedure</th>
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<tbody>
<tr>
<td>Complete blood count, differential, platelets</td>
</tr>
<tr>
<td>Coagulation studies</td>
</tr>
<tr>
<td>Chest radiograph</td>
</tr>
<tr>
<td>Polymerase chain reaction or direct fluorescent antibody of any cutaneous lesions</td>
</tr>
<tr>
<td>Viral culture of oropharynx, nasopharynx, conjunctiva, and rectum</td>
</tr>
<tr>
<td>Viral culture of blood and urine</td>
</tr>
<tr>
<td>Cerebrospinal fluid for analysis (cell count, differential, protein, and glucose)</td>
</tr>
<tr>
<td>CSF for PCR and viral culture</td>
</tr>
<tr>
<td>Electroencephalogram if seizures are suspected</td>
</tr>
<tr>
<td>Computerized tomogram or magnetic resonance imaging if neurologic symptoms are present</td>
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</tbody>
</table>

Adapted from Arvin, Kesson, and the American Academy of Pediatrics.
In the presence of vesicular lesions, the base of the lesion should be scraped and sent for both viral culture and polymerase chain reaction (PCR). The PCR is a rapid genetic amplification technique, which detects the presence of minute quantities of viral DNA.\[29\] It can be performed on blood, cerebrospinal fluid, and mucocutaneous lesions. The PCR test has been shown to be highly sensitive in the diagnosis of herpes infection and has also been shown to be even more reliable than viral culture for CNS and mucocutaneous infections.\[22,40\] Although the presence of a positive PCR is highly predictive of infection, a negative result does not eliminate the possibility of disease and thus, if herpes infection remains high on the differential diagnosis, antiviral therapy should be either initiated or continued.\[31,41\]

Direct immunofluorescent antibody staining detects the presence of the HSV antigen and can also be performed on cutaneous lesions. Although this test is not as reliable as the PCR and both false negatives and false positives may occur, it may be necessary in those situations for which PCR testing is not available in a timely manner.

Besides culturing any cutaneous lesions, viral cultures of the oropharynx, nasopharynx, conjunctiva, and rectum as well as both the blood and urine should be performed.\[2,29,30\] Although it is possible to test for the presence of HSV-specific IgM in the blood through the use of enzyme-linked immunosorbent assay (ELISA) testing, this is not recommended during the newborn period due to a high rate of both false positive and negative results. Only 12% of infected infants will have a positive ELISA test at one week of age and, if one waits until two to six weeks or even 6 to 18 months, 25% of infants who had documented herpes infection will still not have detectable IgM levels. To make matters even more complicated, over 80% of infants whose mothers experienced a herpes infection in the perinatal period were uninfected, but had positive IgG levels due to transplacental delivery of maternal antibodies.\[42\]

Accurately diagnosing herpes meningitis and/or encephalitis can be very difficult. On CSF analysis, one can usually appreciate a pleocytosis with 20 to 100 white blood cells and an elevated protein in excess of 1 g/dL. However, these findings may not be present early in the disease process, and thus withholding antiviral treatment should not be based on a normal CSF profile.\[43\] Viral cultures are notoriously poor in their ability to successfully diagnose herpes meningitis, with less than 50% of CSF viral cultures being positive in infants with HSV meningitis.\[2,3,33\] Historically, the gold standard for the diagnosis of herpes meningitis was brain biopsy, however, due to the invasive nature of such a test, it is rarely performed except at autopsy. Recently, the use of PCR testing of CSF is replacing the brain biopsy as the gold standard for the identification of neonatal herpes meningitis. It has been shown to be extremely reliable with a sensitivity rate of 75 to 100% in the detection of HSV DNA and is considered far superior to viral culturing of CSF.\[22\] However, even PCR testing is negative in 24% of herpes meningitis and may not become positive until later in the disease process and therefore serial testing of PCR may be necessary.\[41,44\]

In infected infants presenting with seizures or other neurologic symptoms, it is recommended that an electroencephalogram (EEG) and either a CT or preferably magnetic resonance imaging is performed as part of the diagnostic procedure.\[22\] The EEG is likely to reveal either the presence of seizure activity or an abnormal background with a paroxysmal pattern, which is very suggestive of HSV encephalitis.\[45\] Neurologic scans may be normal initially in the disease but, after approximately five days,\[46\] typically begin to show focal abnormalities in the temporal lobes, insular cortex, and the gyrus rectus.\[3,47\]

In the late 1970s effective antivirals for treating neonatal HSV were beginning to be used and have since been shown to ameliorate this disease. The first available drug, virdarabine, was studied extensively in the 1980s.\[32,48\] By the end of the decade a study comparing virdarabine and acyclovir showed the latter to be just as effective in treating neonatal HSV.\[32,49\] Acyclovir quickly replaced virdarabine as the drug of choice because of its ease of use.\[50\] There have been a few case reports of newborns with acyclovir-resistant HSV infection. Although this is rare, it must be suspected in those infants who do not respond appropriately or who deteriorate after initial clinical improvement on acyclovir therapy. In these cases foscarnet can be substituted effectively.\[11,40,51\]

Acyclovir is used for the prevention and treatment of HSV and varicella infections and is available in intravenous or oral forms, although there is limited data for oral use in the newborn. Tod and coworkers\[52\] published a study in 2001 describing the pharmacokinetics of oral acyclovir in newborns and children. In this study the inhibitory concentration of acyclovir was greater than 50% for 12 hour during a 24 hour period, thus showing that oral dosing for newborns at
24 mg/kg/g8h is adequate for treating HSV infections.[52] The current recommendation, however, is that acyclovir be administered intravenously.[2]

Acyclovir was approved by the Food and Drug Administration for use in treating neonatal HSV in June 1998.[50] It is a DNA chain terminator and acts as a competitive inhibitor of HSV DNA polymerase.[6,10,53] Acyclovir can cause renal toxicity but this can be prevented or reversed with good hydration. It has also been associated with CNS toxicity when using high doses in the presence of renal failure. Other side effects include nausea, vomiting, and diarrhea.[54] Acyclovir is ineffective in latent infections and does not eradicate virus from the ganglia.[11]

Traditionally the standard dose of acyclovir was 30 mg/kg/day divided three times per day. In 2001 Kimberlin and coworkers.[50] published a paper summarizing the work of The National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group from 1981 to 1997. They briefly described the initial study done during the period 1981 to 1988 showing the safety and efficacy of acyclovir in the treatment of neonatal HSV using standard doses. Continued high mortality and morbidity despite standard therapy for 10 days led to the second study comparing intermediate doses (45 mg/kg/day) of acyclovir with high doses (60 mg/kg/day) for safety, toxicity, and effectiveness. This study, conducted between 1989 to 1997, supported the use of high dose acyclovir and recommended treatment doses are now 60 mg/kg/day divided three times per day for 21 days in Central Nervous System (CNS) and disseminated disease and 14 days for SEM disease.[2,39,50] The most significant side effect of high dose acyclovir was neutropenia, but the study was inconclusive as to whether the severity of disease or the actual dosing was the cause. Neutropenia in all patients resolved during continuation of treatment or after the course and there were apparently no side effects of the neutropenia.[50] Grade three or four nephrotoxicity occurred in only 6% of the patients treated with high dose, and this also could have been attributed to the severity of the disease. In addition, high dose acyclovir was shown not to impede antibody response. There was a statistical significance in mortality in patients with disseminated disease treated with standard and high dosing. Mortality with standard dosing was 61%, intermediate dosing was 57%, and high dosing was 31%.

The prevention of HSV infection in the newborn has received considerable attention. In 1999 the American College of Obstetricians and Gynecologists (ACOG) developed a practice model for the management of herpes in pregnancy.[55] Universal screening is not recommended as this is inaccurate and not cost effective. The ACOG recommendations included the following points:

- Primary infection during pregnancy should be treated with antivirals; this reduces viral shedding and promotes healing of lesions
- Cesarean delivery for those with primary infection and lesions at delivery
- Treatment for pregnant women beyond 36 weeks' gestation with a primary infection
- Cesarean delivery for recurrent HSV infections with lesions or prodromal symptoms at delivery
- Expectant management of patients with preterm labor or prolonged premature rupture of membranes and lesions may be warranted
- Consider treatment for women at or beyond 36 weeks' gestation with recurrent HSV infection; this will decrease clinical occurrences and possibly the need for cesarean section (C/S)

Even though these recommendations increase the likelihood of cesarean section from 23 to 85%, their use decreases vertical transmission of HSV to the newborn by 50%.[16] Treatment with acyclovir in pregnancy is a reasonable option as several studies have suggested it is free of teratogenic effects.[46,56] Acyclovir is concentrated in the amniotic fluid but does not accumulate in the fetus.[57,58]
No single method has proven effective in preventing transmission of genital herpes to newborns. Several studies have looked at various methods to predict which women were at highest risk. Attempts at using antenatal viral cultures to predict the exposure from asymptomatic viral shedding, suppressive acyclovir therapy during the last weeks of pregnancy, or universal screening of all pregnant women for HSV-2 have been either unsuccessful or too costly.[59-61]

In 1996, Randolph and associates studied, from a health care payer’s perspective, four methods to prevent vertical transmission of HSV from pregnant women to infants.[62] The four methods were A, C/S if lesions were present; B, acyclovir prophylaxis in late pregnancy and C/S if lesions were present; C, acyclovir prophylaxis in late pregnancy and vaginal delivery if lesions were present but with screening and follow up of exposed infants; and D, no intervention. This study showed that acyclovir prophylaxis late in pregnancy to prevent genital herpes outbreaks in women with recurrent infection would prevent more neonatal herpes infections and save money over the current strategy at that time of no acyclovir and C/S when lesions were present. Although this strategy may reduce the number of neonatal HSV infections in women with recurrent HSV, it may not change the overall incidence of neonatal herpes, as most infections are acquired from women with primary herpes.

Barnabas and associates[12] in 2002 reported the results of a health care economic analysis evaluating the use of prophylactic acyclovir on reducing neonatal HSV infection. In the first group (P1) no intervention other than normal pregnancy costs were employed; the second group (P2) followed the ACOG guidelines; and the third group (P3) consisted of treating partners with acyclovir, counseling and screening all pregnant women and their partners, and performing C/S for women with herpes at time of delivery. For this study the estimated yearly number of neonatal cases of HSV for group P1 was 169. This number was reduced to 155 in group P2 and to 31 in group P3. Screening and therapy (P3) prevents 80% of cases compared with the existing ACOG guidelines but was shown not to be cost effective. This study using the human capital approach, which uses estimates of lost wages to evaluate morbidity and mortality, found that, while group P3 had the greatest impact on neonatal herpes incidence, it was not cost effective. This approach, however, does not account for neonatal mortality and the value of an infant’s life.

HSV infection in the newborn period can be a significant source of mortality and morbidity. The prognosis of HSV infection is related to classification of the disease and the early initiation of treatment. Before antiviral therapy, mortality was 50% for CNS disease and 85% for disseminated disease. With the use of high dose acyclovir therapy, mortality decreased to 4% for CNS disease and to 29% for disseminated disease.[2] The mortality rate of SEM disease is 0% unless diagnosis and treatment is delayed.[41] Failure to recognize and treat SEM disease can quickly progress to CNS and/or disseminated disease. Other predictors of mortality include prematurity, pneumoentisis, DIC, and coma.[6]

Although there have been great strides in the diagnosis and treatment of HSV infection in the newborn, this disease continues to be associated with significant long-term sequelae, including learning disabilities, cerebral palsy, blindness, and persistent seizures.[2,20,29] Kimberlin and coworkers[2] reported that, with the use of high dose acyclovir, normal development at 12 months occurred in 98% of infants with SEM disease, 30% with CNS disease, and 75% with disseminated disease. Among the patients diagnosed with CNS disease, seizures at initiation of treatment and the detection of HSV DNA by PCR analysis in the CSF following treatment significantly increases the incidence of abnormal development.[2,31]

There is a direct correlation between development of neurological deficits and frequency of cutaneous HSV recurrences.[19,29] The use of suppressive oral acyclovir at 300 mg/m² three times per day for the first six months decreases the risk of reoccurrence. However, at this time there are no data to support an improved prognosis and therefore the use of suppressive therapy should only be used as an investigational therapy.[40] In addition, although antiviral therapy is the only current treatment for HSV infection, the development of a vaccine and/or passive immunotherapy is currently under investigation.

Despite advances in the management of neonatal HSV infection, no progress has been made in decreasing the time interval between onset of symptoms and initiation of treatment. Early diagnosis and treatment of the infection can
have a significant effect on the mortality and morbidity of this disease. A delay in diagnosis may occur because of a negative maternal history, as 60 to 80% of women who acquire primary HSV infection during pregnancy are asymptomatic at delivery. Delay in diagnosis also occurs since symptoms of HSV can often resemble those of neonatal bacterial sepsis. Clinicians caring for newborns either in the hospital or in outpatient settings must have a high index of suspicion for neonatal HSV infection to ensure prompt diagnosis and treatment and therefore positively impact the outcome of neonatal HSV.

References


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