

PERINATAL HERPESVIRUS INFECTIONS

WILLIAM J. BRITT*

Perinatal viral infections remain a major cause of newborn infant morbidity and mortality. Although maternal infection with many of the viral agents recognized as causes of disease in the fetus and/or newborn infant are not associated with significant maternal disease, the recognition that maternal immunity could limit virus transmission and disease in the newborn infant provided a strong rationale for development of vaccines to limit the morbidity of perinatal infections. Vaccines such as those against rubella virus have nearly eliminated rubella as a cause of disease in the fetus and newborn infant. Herpesviruses are also common causes of perinatal infections and can cause devastating disease. Infection with herpes simplex virus during the neonatal period continues to represent an important cause of disease and with an increase in the incidence of genital herpesvirus infections will likely continue to be a cause of disease in newborn infants. Fortunately, effective antiviral therapy is available, yet the delay in recognition of infected infants continues to represent an unresolved issue in the treatment of infected infants. Although previous attempts to vaccinate women against herpes simplex virus infection have been unsuccessful, newer vaccine preparations and adjuvant are being tested. Human cytomegalovirus is recognized as the most frequent cause of fetal virus infection. Up to 10% of infected infants can manifest disease and develop long term neurologic sequelae following this intrauterine infection. Early natural history studies suggested that this congenital infection could be a vaccine preventable disease. However, more recent studies have argued that the majority of infants infected in-utero was not protected by maternal immunity that followed natural infection. Thus, it may be necessary to reexamine the role of immunity in this maternal/fetal infection. Antiviral therapy in the postnatal period has provided some minimal benefit and if similar therapy could be delivered to the infected fetus, it could potentially limit central nervous system damage in-utero and the development of long term sequelae.

Descriptors: PERINATAL INFECTION, HERPESVIRUS

Introduction

Maternal infection with a number of viruses during pregnancy and in the peripartum period can result in transmission of the virus to the fetus and newborn infant. In some cases these infections in newborn infant can result in significant morbidity and mortality, depending on the specific viral agent, the age of virus acquisition, and perhaps more importantly, characteristics of the maternal infe-

ction associated with transmission to the fetus or newborn infant. Each of these factors can contribute to both the incidence and outcome of infection in the fetus or newborn infant, but features unique to the natural history of each of these viral infections allow only a limited number of generalizations to be made about this group of infections. Perinatal infections can be divided into those acquired in-utero by the developing infant and present at birth (congenital infection) and those acquired at the time of birth (peripartum). A much smaller number of neonatal infections are acquired in the postnatal period through exposure to infected caretakers who are often individuals other than the mother. A list of viruses associated with perinatal infections is provided in table 1.

These agents are listed in an approximate order of their frequency as causes of infection and disease in fetuses and infants in the US. However, the relative importance of these agents as a cause of disease in infants from underdeveloped countries and countries with transitional economies is not well documented. Undoubtedly, HIV and hepatitis viruses likely are more frequently observed in populations from non-first world countries, particularly as causes of perinatal infections. For this brief overview of perinatal infections, we will discuss neonatal herpes simplex infections as an example of perinatal infection and CMV as an example a virus that commonly causes both congenital and perinatal infections.

*University of Alabama at Birmingham
Department of Pediatrics

Address:
William J. Britt, M. D.
Professor of Pediatrics, Microbiology
and Neurobiology
University of Alabama at Birmingham
Department of Pediatrics
1600 6th Avenue South
Children's Harbor Building 107
Birmingham, AL 35233-1711

Table 1
Viral agents associated with perinatal infection
 Tablica 1.
Virusi uzročnici perinatalnih infekcija

Congenital Infections	Perinatal/Postnatal Infections
Cytomegalovirus (CMV)	HIV
Parvovirus	Herpes Simplex Virus (HSV)
HIV	Hepatitis B Virus
Herpes Simplex Virus (HSV)	Hepatitis C Virus
Varicella-Zoster Virus (VZV)	Varicella-Zoster Virus (VZV)
Hepatitis B virus	Enterovirus
Hepatitis C virus	Respiratory Viruses
	Rotavirus
	CMV

Neonatal herpes simplex virus infections

Natural History of Neonatal Herpes Simplex Virus Infections

Herpes simplex virus is the prototypic virus of the alpha-herpesvirus subgroup of the family of herpesviruses. This group of viruses includes both HSV-1, HSV-2, and varicella-zoster virus (VZV) and as a group share neurotropism and the propensity to establish latent infections as one mechanism for virus persistence. HSV is a large double stranded DNA virus with a complex and highly regulated replication program that if fully expressed, leads to cell death. The virus encodes a number of immunogenic proteins that are targets of both innate and adaptive immunity, including virus neutralizing antibodies directed against the envelope glycoproteins. Protective immune responses against HSV have been well described in animal models of HSV infections, including both virus specific CD8+ CTL and virus neutralizing antibodies (14). Similarly, studies in humans have shown that the presence of both CD4+ and CD8+ virus specific T lymphocytes correlates with a reduced number of viral reactivations from latency and severity of disease. Correlative data from clinical studies have suggested that antiviral antibodies limit transmission to newborn infants and anecdotal evidence suggest antiviral antibodies can

limit disease in infected newborn infants (30, 39).

Further evidence of a potential role for antiviral antibodies in protective responses to HSV infections in the perinatal period has been suggested by the large body of evidence demonstrating the protective activity of varicella-zoster virus (VZV)-neutralizing antibodies in perinatal acquired VZV infections. These studies have provided the rationale for the use of varicella immune globulin (VZIG) in the prevention/treatment of this virus infection of the newborn infant. Herpes simplex virus 1 and 2 share considerable genetic homology and are co-linear over most their genomes. Extensive antigenic cross-reactivity can be documented between proteins encoded by each virus and as a result, cross-reactive antibodies can be detected against both viruses. Thus, simple serologic assays cannot differentiate between HSV-1 specific versus HSV-2 specific antibody reactivity. However, a single envelope glycoprotein, gG, appears to induce specific antibody responses reactive with gG of HSV-1 and gG of HSV-1. This antigenic characteristic of gG allows for the serologic differentiation of infection with HSV-1 and/or HSV-2.

The incidence of neonatal herpes simplex infection ranges between from 1/3,000-1/20,000 live births, depending on the location in the world. The most extensive studies have been done in the

US and current estimates of the incidence of neonatal herpes virus infection is approximately 1/3,200 live births yielding an estimated 1,500 infected infants per year in the US (17, 26). Although it is a certainty that asymptomatic infections or infections limited to a single cutaneous or mucosal site occur, clinical studies from the early 1980's revealed that approximately 70% of infants with mucocutaneous HSV infections that were not treated, progressed to visceral and CNS involvement (54). In addition, more recent analysis of specimens from patients enrolled in studies of antiviral therapies of the 1980s have revealed that neonatal infections that were thought to involve skin or mucosal sites at the time of diagnosis likely included a spectrum of disease including, mucocutaneous infections and more limited visceral involvement (25). Thus, all neonatal HSV infections should be considered life and organ threatening infections.

The routes of transmission HSV to the newborn include blood borne infections and contact with oral and genital secretions. Less than 5% of infants with neonatal herpes virus infection acquire HSV in-utero, presumably as a result of maternal viremia. The vast majority (>85%) of infected infants acquire HSV at the time of delivery following exposure to infectious virus in the genital tract. In the remainder of cases virus is acquired in the postpartum period after exposure to virus from an infected caretaker. In the vast majority of cases of neonatal HSV infections, newborn infants are infected during vaginal delivery. Genital tract shedding of HSV can result from at least three types of maternal genital tract infection, a 1st episode primary infection, a non-primary 1st episode HSV infection in a women with preexisting infection, or a recurrence/reactivation of preexisting infection (Table 2).

The epidemiology of maternal genital tract infection with HSV is complex but decades of study have provided a reasonably clear understanding of the natural history of this infection. Genital tract infections can be caused by either HSV-1 or HSV-2. In the US, the ratio of HSV-1/HSV-2 infections is approximately 2/5, yet in other areas of the world the ratio

Table 2
Risk of maternal HSV transmission and classification of maternal infection

Tablica 2.
Rizik maternalnog prijenosa HSV i klasifikacija maternalne infekcije

Classification of maternal infection ¹	Rate of transmission to newborn infant ²
1st episode primary infection	50%
1st episode non-primary infection	25%
recurrent infection	2%

¹1st episode denotes 1st infection with HSV. Infection of women with previous HSV-1 infection with 1st infection with HSV-2 (or vice versa) is defined as 1st episode non-primary infection. Recurrent infection denotes women with seroreactivity for both HSV-1 and HSV-2

²Rate of transmission of women asymptotically shedding HSV in genital tract at time of delivery (17)

is nearly 1/1. The spread of these viruses is through genital-genital or oral-genital contact, the latter route of transmission is thought to account for the increase in genital HSV-1 infections that has been observed in the US. Infections in women without prior HSV-1 or HSV-2 infections is classified as 1st episode primary infection, infection of women with prior HSV-1 infection with HSV-2 or vice versa is classified as a non-primary 1st episode infection, and recurrence of a preexisting infection is classified as a recurrent infection. As would be expected each type of infection is associated with different levels of maternal immunity and the amount and duration of virus in the genital track. Therefore, it is not surpris-

ing that the rate of transmission differs between each type of maternal infection (Table 2). First episode primary maternal infections represent the greatest threat to the newborn infant and approximately 50% of these women will transmit virus to their offspring. In contrast, transmission to the offspring occurs in about 2% of cases of seropositive women with recurrent infection. Women with 1st episode non-primary maternal infections transmit virus to their offspring at an intermediate rate of approximately 25%.

These findings argue strongly that maternal immunity is a critical determinant in transmission of virus to the newborn infant and have provided a rationale for vaccine development for pre-

vention of this perinatal infection. Additional evidence for the role of maternal immunity in limiting transmission of HSV to the offspring include the finding that overall 0.20-0.39% of HSV infected women excrete virus in the peripartum period, whereas women with proven recurrent HSV genital tract disease excrete virus at much higher rates that range between 0.77-1.4%. Because transmission is less frequent in this latter population, it has been argued that although a robust maternal immune response fails to limit maternal virus excretion, it can limit perinatal HSV transmission.

Other factors that influence the rate of HSV transmission to the newborn infant include, maternal antibody status (see above), duration of rupture of membranes, mucocutaneous injuries (scalp electrodes), and the mode of delivery (cesarean section versus vaginal birth). The maternal antibody status is related to the type of maternal infection and has been most closely correlated to the presence of virus neutralizing antibodies. Because HSV entry and infection requires viable cells of an epithelium or a loss of integrity of the cutaneous barrier, damage to the skin caused by a scalp electrode can provide a site of entry for HSV. Finally, delivery of the infant by cesarean section can in almost all cases limit exposure to HSV in the genital track and a recent study has provided definitive evidence that cesarean section can prevent neonatal HSV infection in offspring of women that are excreting HSV in their genital tract at the time of delivery (5, 17). Yet there are reports of neonatal herpes in infants born following cesarean section with intact membranes (53).

Clinical Presentations of Disease

Nearly three decades ago physicians classified the presentations of neonatal herpes virus infection into three categories of disease:

- lesions limited to skin, eye, and mouth (SEM);
- disseminated infections with visceral involvement;
- CNS infections.

Table 3
Clinical findings in infants with neonatal HSV infections

Tablica 3.
Klinički nalazi u novorođenčadi s neonatalnom infekcijom HSV

Clinical Findings	Disease Classification		
	SEM ¹	CNS ¹	Disseminated ¹
Skin vesicles	83%	63%	58%
Lethargy	19%	49%	47%
Fever	17%	44%	56%
Conjunctivitis	25%	16%	17%
Seizures	2%	57%	22%
Pneumonia;coagulopathy	0	0	34%

¹Skin, eye, and mouth involvement (SEM) is present in about 50% of babies as only clinical manifestation of infection. Central nervous system involvement occurs in about 30% of infants and although these babies not infrequently have skin lesions, they also exhibit symptoms consistent with CNS dysfunction or laboratory evidence of CNS disease. Disseminated infection occurs in about 25% of infected infants and these babies have widely disseminated disease, often with CNS involvement

Each of these categories of disease has been associated with a different age of onset, prognosis, and long term outcome (table 3) (25, 26). With the advent of more sophisticated diagnostic methodologies, many of the arbitrary assignments of specific clinical presentations have proven incorrect. As an example, in a large study of neonatal HSV infections, 24% of patients originally classified as having SEM disease were shown to have evidence of HSV DNA in their CSF at the time of diagnosis indicating that the clinical classification of these infants was inaccurate. In addition, it could also be argued that these cases, infection began as SEM involvement and subsequently spread to the CNS. This observation argues that infants with cutaneous vesicular eruptions that are consistent with HSV should be treated immediately with appropriate doses of acyclovir, regardless if diagnostic laboratory services are available. The clinical findings of neonatal herpes infection are provided in table 3.

Disseminated neonatal HSV infections represented the most common presentation of disease prior to the availability of effective antiviral therapy, presumably secondary to the dissemination of localized infection. The incidence of this form of the disease has fallen to about 25% of the total cases of neonatal HSV infections presumably because early clinical recognition and institution of antiviral therapy has become standard of care in most regions of the developed world. Infants with disseminated HSV infections present for medical evaluation in the first 2 weeks of life, a time frame that is slightly earlier than infants with CNS disease who usually present with disease in the 3rd week of life (25). Most infants with disseminated HSV infection present with cutaneous lesions, although up to 20% have no clinical evidence of cutaneous disease at presentation. Over 50% of infants with disseminated disease will have CNS involvement. The mortality rate from untreated disseminated neonatal HSV infection is approximately 85-90% with infants often exhibiting severe coagulopathies, hepatitis, and pneumonia. The latter manifestation of neonatal HSV infections is an ominous clinical sign and almost always is associ-

ated with the demise of the newborn infant. Infants with CNS involvement are at risk for neurodevelopmental abnormalities secondary to the necrotizing encephalitis seen with HSV infection of the brain.

Central nervous system infection with HSV in the neonatal period occurs in about 30% of infants with neonatal HSV infection. Typical presentations include fever, seizures, lethargy, irritability, poor feeding, and other signs and symptoms consistent with CNS inflammation. Similar to the presentation of disseminated neonatal HSV infections, about 70% of infants with CNS disease will have cutaneous evidence of HSV infection. Mortality and morbidity in these infants is associated with the loss of brain tissue secondary to this necrotizing infection. Early therapy can limit disease in these infants but HSV infection of the CNS results in irreversible damage and deficits associated with the loss of normal neurodevelopmental function in survivors. As will be discussed in the following sections, the presence of HSV DNA in the CSF at the clinical presentation in infants with any of the disease categories represents a significant risk factor for the abnormal neurodevelopment.

The final disease category includes infants presenting with skin, eye, and mouth (SEM) involvement. This group of infants likely contains an additional subgroup of infants with asymptomatic involvement of organ systems other than the skin or mucus membranes. Overall, infants with this form of the disease represent about 50% of infants with neonatal HSV infections (25). In addition, this group of infants also has the best outcome if treated early with antiviral therapy. All newborns will survive and all will have a normal neurodevelopmental outcome if adequately treated early in the course of the disease. Cutaneous reactivations of HSV following resolution of primary disease are common in this group of infants and pose a dilemma for most clinicians caring for these patients. Previous studies have described patients with cutaneous reactivations that went on to develop CNS disease. These observations initially lead to the treatment of reactivations with systemically admini-

stered acyclovir and eventually to suppressive therapy in which infants were placed on daily acyclovir for at least the first 6 months of life. The optimal management of these infants has yet to be defined from a well controlled clinical study and the care of each patient is dependent on the experience of the patient's physician.

Diagnosis

The diagnosis of neonatal HSV infection requires a high index of suspicion, particularly because early institution of antiviral therapy can dramatically alter the outcome of HSV infection in the newborn. Unfortunately, the non-specific presentations of infants without obvious cutaneous findings often result in a delay in the diagnosis of neonatal HSV infection. This is reflected by a study that noted that the interval between onset of symptoms and the initiation of antiviral therapy has not significantly changed over a 16 year period. The diagnostic evaluation of an infant with suspected neonatal HSV infection should include virus cultures of any vesicular rash, oropharynx, conjunctiva, urine, rectum, and cerebrospinal fluid. In addition, polymerase chain reaction (PCR) analyses of the CSF and relevant specimens have been shown to be useful in the detection of HSV DNA. If disseminated disease is suspected, evaluation of liver function, coagulation function, and chest radiograph should be obtained. Imaging of the brain, either CT or MRI can provide evidence of CNS involvement.

Specific diagnostic approaches for the diagnosis of neonatal HSV infections include serologic testing, virus cultures, and PCR amplification of HSV DNA. Serologic assays are of little value in the diagnosis of neonatal HSV infection secondary to the presence of transplacentally acquired maternal anti-HSV antibodies. In contrast, isolation of virus from skin lesions or mucus membranes provides a definitive diagnosis. In contrast to CMV, HSV can often be detected in cell culture within 24-48 hours after inoculation. Once typical HSV cytopathic effects are observed in cellular monolayer, virus can be typed by either PCR

or immunofluorescence to determine if the virus is HSV-1 or HSV-2. Isolation of virus from mucocutaneous sites is more often successful than from the CNS, yet virus can be recovered from the CSF in almost 40% of infected infants with CNS disease.

Perhaps the most significant advance in the diagnosis of neonatal HSV infection has been the application of PCR. Overall, this technique has a reported sensitivity of between 100%-80% and specificity between 100%-70%. Although there has been reported variation in the sensitivity and specificity of PCR based assays between different laboratories, in general if specimens are properly collected and processed in laboratories with sufficient experience in PCR based diagnostic techniques, the results of this diagnostic assay are reliable. More importantly, results from this assay can provide very useful information for clinical management of HSV infected newborn infants, particularly in the management of CNS infection. The approach of using PCR analysis of the CSF at the initiation of antiviral therapy and at the end of therapy has become routine in most centers. The failure to eliminate HSV DNA from the CSF after an appropriate course of acyclovir has been associated with a poor outcome, including death (25, 27). Thus, infants who continue to have HSV DNA in their CSF at the end of therapy should continue therapy until the PCR is negative. Finally, it is important to note that a negative PCR must be correlated with the clinical parameters of the patient and, as with all laboratory diagnostic assays a negative result must be interpreted in the context of other laboratory and clinical findings.

Treatment

The outcome of infants with neonatal HSV infection is described in table 3. In the period of time prior to effective antiviral therapy, about 50-85% of infants died by 1 year of age, with the higher mortality seen in infants with disseminated infection. Current recommendations are 60mg/kg/day of intravenous acyclovir given for 21 days and 14 days for infants with disease felt to be limited

to the SEM. Treatment with this dose of acyclovir has resulted in a mortality rate of 29% for disseminated disease, 4% for CNS disease, and no mortality for disease limited to SEM (25, 28). The long term outcome of infants with HSV infection has also improved but infants with CNS disease who present with evidence of CNS dysfunction including seizure activity remain at risk for neurodevelopmental abnormalities. Infants with disease limited to the SEM that are treated with appropriate doses of acyclovir have no reported neurodevelopmental abnormalities (28).

Prevention

Several approaches have been described to limit the transmission of HSV to the newborn infant. Because primary maternal infections represent the greatest risk for HSV transmission to the newborn infant, limiting maternal virus acquisition during pregnancy can also be expected to limit infection of the newborn. It has been estimated that about 3.7% per year of women who are seronegative for HSV acquire the virus from seropositive sexual partner, suggesting that if such discordant couples could be identified, it is conceivable that transmission to the pregnant women could be modified (16). Unfortunately, the vast majority of individuals have asymptomatic genital HSV and orolabial HSV infection, thus it would be necessary to carry-out universal serologic screening for HSV antibodies to identify such discordance between sexual partners. Other approaches are more proximal to the delivery of the newborn infant. These include caesarean delivery of women with genital lesions consistent with HSV infection and/or a prodromal syndrome consistent with genital HSV infection (5).

However, several studies have shown that the vast majority of HSV infected newborn infants are born to women without a history of genital HSV infection (53, 56). Cost-benefit analyses of the use of cesarean delivery to prevent neonatal HSV infection have not provided a convincing rationale for cesarean delivery of infants to reduce the frequency of neonatal HSV disease (40). An

alternative approach, antiviral prophylaxis during pregnancy, has been suggested as possible prophylaxis for neonatal HSV infection. Although virus excretion can be suppressed with acyclovir or valacyclovir during pregnancy, it remains uncertain if this approach can interrupt virus transmission. Finally, a trial of a subunit vaccine to prevent genital HSV infection has been undertaken by the National Institutes of Health of the US and its corporate partner, GlaxoSmithKline. It appears that this vaccine offers some benefit only in women who are seronegative for both HSV-1 and HSV-2.

Perinatal Human Cytomegalovirus Infections

Natural history of perinatal human cytomegalovirus infections

Infection with human cytomegalovirus (CMV) is commonplace and in the most of the world, universal by early adulthood. Rarely is infection in an immunocompetent host associated with clinical symptoms or disease; however, this virus can cause severe and life-threatening infections in immunocompromised hosts. Infection of the developing fetus and the extremely premature infant represent two patient populations that are at risk for severe HCMV infections, presumably secondary to the developmental immaturity of their immune system. Acquisition of CMV by the fetus and newborn infant can occur by several mechanisms, all of which are similar to that described for HSV. The developing fetus can be infected in-utero by a blood borne infection presumably through infection of the placenta following maternal viremia or possibly through extension of an ascending infection from the maternal genital track. In the peripartum, infants can be infected during delivery through exposure to virus containing genital secretions. Finally, in many parts of the world infants are most commonly infected following ingestion of virus containing breast milk. In rare cases, CMV is transmitted to premature infants following blood transfusions or ingestion of breast milk and in some cases such infections can result in organ-threatening and life-threatening infections.

Table 4
Maternal risk factors associated with delivery of congenitally CMV infected baby

Tablica 4.
Faktori rizika majki udruženi s rođenjem djeteta inficiranog s CMV

Risk Factor
Young age (<20 years of age)
Increased rates of CMV infection
Increased rates of cervical CMV excretion
History of STI
Exposure to young children
Multiple sexual partners

Human cytomegalovirus is the largest and structurally the most complex member of the herpesvirus family. Its genome contains approximately 260000 base pairs of DNA, making it approximately nearly twice the size of HSV and about 25 times the size of the human immunodeficiency virus (HIV) (33). The virus encodes a plethora of proteins whose functions include not only replication of viral progeny but in addition, modification of the host cell environment to optimize virus replication. Perhaps more importantly in the pathogenesis of HCMV infections is the capacity of CMV gene products to modify the milieu surrounding the infected cell to both enhance virus spread to other cells and to limit immune recognition of virus infected cells leading to virus persistence within the host.

From studies of various immunocompromised patient populations, it is clear that host-derived antiviral innate and adaptive immunity are required for control of CMV replication and prevention of disease. Studies from animal models of CMV infection have clearly demonstrated the critical role of virus specific CD8+ cytotoxic T lymphocytes and CD4+ T lymphocytes in resistance to CMV infection (24, 31, 37, 38, 51). Studies in allograft recipients have also demonstrated the importance of these effectors of the adaptive immune response to the control and clearance of virus infection (6, 41, 52). A critical role for natural killer cells (NK) and interferons in resistance to CMV infection and di-

sease has been shown in rodent models of CMV infection, but similar findings in human infection have as of yet, not been convincingly demonstrated. Finally, antiviral antibodies have been conclusively shown to limit virus dissemination in small animal models and in non-human primate models of CMV infection (18, 23, 46). Studies in humans have also demonstrated an important role of antiviral antibodies, particularly virus neutralizing antibodies in limiting virus dissemination and disease (8, 11, 44, 45, 47, 48).

Congenital CMV infections

As was noted above, perinatal CMV infections of clinical significance are limited to those infections acquired in-utero and in infrequent cases, infection of extremely premature infants. This discussion will focus almost entirely on intrauterine infection of the developing fetus because these infections can potentially represent a relatively frequent cause of disease in the newborn infant. Because this infection is transmitted from the pregnant mother to the developing fetus, understanding the pathogenesis of CMV infection in the pregnant woman is key to understanding the pathogenesis of congenital CMV. It is believed that maternal immunity plays a major role in both the transmission of CMV to the fetus as well as the virulence of the ensuing infection. However, several experimental findings as well as clinical observations have suggested that once the fetus is infected, the immune status of the mother may play only a limited role in determining the outcome of the fetal infection. The incidence of congenital CMV infection (present at birth) ranges from <0.1% -2-3% of live births depending on several characteristics of the maternal delivery population (Table 4). This observation suggests that maternal immunity is incomplete, similar to observations reported in studies of the perinatal transmission of HSV (see table 2). Transmission rates for women undergoing primary infection that occurs shortly before or during pregnancy range between 25-75%, with a rate of 40% being an average of most of the reported studies (49).

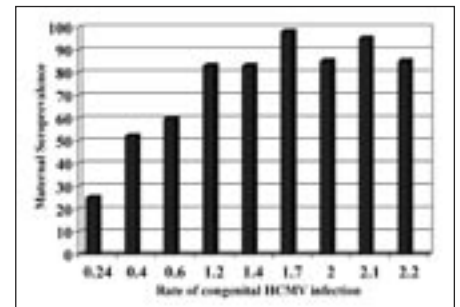


Figure 1
Congenital CMV infections increase as maternal CMV seroprevalence increases

Slika 1.
Kongenitalna infekcija CMV povećava se s porastom seroprevalencije CMV

In contrast, women with previous CMV infections prior to conception have transmission rates that range from 0.1%-7% (49). The broad range in these transmission rates is related to unique characteristics of the maternal delivery population. Thus, it appears that in some populations pre-existing maternal immunity can reduce virus transmission by about 20 fold. However, one of the more surprising features of congenital CMV infection is the relationship between maternal CMV infection and the incidence of congenital infection in the offspring of the population. Numerous studies have demonstrated a positive correlation between rates of CMV infection in a delivery population and incidence of congenital CMV infection such that as more women are infected, the rate of congenital CMV infection increases (Figure 1).

An analysis of these data suggest that in populations with increased CMV seroprevalence, most congenital CMV infections arise from maternal reinfections or reactivation of existing infections whereas in populations with lower rates of CMV infection, most cases of congenital CMV appear to follow primary maternal infections. These observations suggest that exposure to CMV is a major determinant of maternal infection and intrauterine transmission, not maternal immunity. This observation has obvious implications for vaccine development (see below).

Community sources of maternal infection with CMV have been defined by natural history studies and include

Table 5

Clinical and laboratory findings in infants with clinically apparent (symptomatic) congenital CMV infection (1)

Tablica 5.

Klinički i laboratorijski nalazi u novorođenčadi s klinički izraženom kongenitalnom infekcijom CMV (1)

Clinical or Laboratory Finding	% with abnormality
Prematurity	34%
Small for gestational age	50%
Petechiae	76%
Jaundice	67%
Hepatosplenomegaly	60%
Neurologic abnormalities	68%
Elevated liver transaminases	83%
Thrombocytopenia (<100,000/mm ³)	77%
Direct hyperbilirubinemia	69%
Increased CSF protein (.120mg/dl)	46%

¹Frequency determined by findings of 106 infants with symptomatic congenital CMV infection. Table modified from Boppana, et al (10)

exposure to young children and sexual exposure. Young children represent an important source of CMV as infants infected in-utero, perinatally, or even in early infancy can excrete significant quantities of virus in their urine and saliva. Spread of CMV between infants and children in group care settings has been shown to occur and spread to caretakers of children in group care centers has also been well documented (1, 2, 34, 35). In addition, young children have been shown to be sources of infections in families, including spread of virus from children to susceptible parents (34, 35). A second major source of virus infection in the community is sexual exposure. Sexual transmission of CMV is common and CMV is classified as a sexually transmitted infection (STI). Interestingly, re-infections with a new strain of CMV occur frequently and the risk of re-infection appears most closely correlated with exposure to CMV. Thus, many individuals likely harbor multiple strains of CMV acquired through different exposures to the virus. As noted immediately above this finding also has important consequences in the design of vaccines to limit CMV infection and disease.

Approximately 10-15% of congenitally infected infants will have clinical

findings consistent with congenital CMV infection. These signs can include hepatosplenomegaly, petechial rash, and microcephaly. Laboratory abnormalities associated with congenital CMV infections include elevated transaminases consistent with hepatocellular damage, thrombocytopenia, periventricular calcifications, retinitis, and abnormal hearing. A summary of the clinical and laboratory findings of congenital CMV is listed in table 5. About 60-80% of infants with symptomatic infections develop sequelae as compared to 8-18% of infants with asymptomatic infection (10, 49). Long term sequelae are most commonly associated with neurodevelopmental abnormalities with the most common long term sequelae being hearing loss (19, 20).

An estimated 10-15% of infants of congenitally infected infants will have hearing abnormalities ranging from mild to profound loss of hearing (19, 55). Perhaps more importantly, in a significant number of infants with congenital CMV infection hearing loss either progresses during infancy or develops late in early infancy. Thus, infants with hearing loss following congenital CMV infections can be misidentified as having normal hearing in universal hearing screening

programs carried out in the neonatal period. The frequency of congenital CMV infection and the relatively high rate of hearing loss in infants with congenital CMV have lead to the speculation that congenital CMV infection may rank only second to familial or genetic etiologies of hearing loss (21, 22). The risk of symptomatic CMV infection in an offspring of a pregnant woman with CMV infection has previously been thought to be limited only to women with a primary infection, which is acquisition of an infection in a woman without preexisting immunity. More recent studies have revisited this concept and an analysis of a large number of infants with symptomatic congenital CMV infection have suggested a nearly equivalent number of infants with symptomatic infection were born to women with preconceptional immunity to CMV (non-primary infection) as were born to women with primary CMV infection (Table 6). These observations have suggested that intrauterine infections leading to clinical disease in newborn infants can be independent of the type of maternal infection. Other risk factors for severe congenital infections, particularly CNS damage, include maternal infection in late 1st trimester and early 2nd trimester of gestation (50). Finally, a more recent study suggested that primary maternal infection during pregnancy and not in the peri-conceptional period is more likely to result in intrauterine infection and disease (43).

The virologic characteristics of congenital CMV infections have provided some insight into the pathogenesis of this intrauterine infection. In general, it appears that disease in the fetus and newborn infants can be most closely correlated with virus replication. This was first illustrated by studies of virus excretion in infants with symptomatic and asymptomatic congenital infections which demonstrated higher levels of virus excretion for longer periods of time in infants with symptomatic infections. More recent studies have also confirmed these findings and have utilized PCR analysis of blood specimens from congenitally infected infants with and without clinical findings of CMV infection (7, 13). These data confirm that higher le-

Table 6
Outcome of infants delivered to women with primary and non-primary CMV infections during pregnancy

Tablica 6.
Ishod novorođenčadi kod majki s primarnom i neprimarnom infekcijom CMV tijekom trudnoće

	Primary Infection	Non-Primary Infection
Symptomatic Congenital Infection	11/59 (19%) ¹	13/66 (20%)
	9/30 (30%) ²	9/32 (28%)
Asymptomatic Congenital Infection	48/59 (81%) ¹	53/66 (80%)
	21/30 (70%) ²	25/32 (72%)

¹Infants enrolled in studies at University of Alabama Birmingham following a primary and non-primary maternal infection. Data kindly provided by Dr. S. Boppana

²Modified from Ahlfors, et.al (4)

vels of viral DNA in blood correlate with the severity of clinical disease. However, it is of interest to note that the severity of CNS disease is not correlated with the level of viral DNAemia. Several explanations could account for this observation including the timing of fetal infections resulting in CNS disease and/or the possibility that the natural history of CNS infection is independent of the infection in the liver and spleen.

Perinatal infection with CMV can occur at the time of delivery and following exposure to infected breast milk or rarely, following exposure to CMV infected blood products. In the overwhelmingly majority of cases, perinatal CMV infection in term infants is not associated with clinical disease and long term CNS sequelae have not been described in infants infected either at birth in the perinatal period. However, cases of severe, life-threatening CMV infections in premature infants have been described in infants given CMV infected breast milk.

Breast milk excretion is frequent and approaches 100% in CMV infected women and a subset of premature infants can develop clinically significant infections following ingestion of CMV infected breast milk. In most well described cases of symptomatic infection following breast milk exposure, the premature infants are often extremely premature and have received little maternal IgG as a result of their prematurity. A similar observation was made over 3 decades ago but in this report, premature infants born to CMV

non-immune women acquired infection following transfusion of CMV infected blood products (57). In this original report, the presence of antiviral antibodies was associated with protection from disease but not infection (57). Thus, perinatal infection with CMV is extremely common and in almost cases is not associated with disease or long term sequelae. In rare cases, CMV infection in newborn infants that lack sufficient amounts of circulating antiviral IgG can develop symptomatic disease. In either case, these infants excrete large amounts of CMV in the urine and saliva for months to years following infection, making them reservoirs for CMV infection of parents, siblings, caretakers and other children.

Diagnosis

In the past, the diagnosis of congenital and perinatal CMV infections was readily accomplished by virus isolation from either the saliva or urine. Because infants infected in utero and in the perinatal period excrete large amounts of virus (>10³ infectious units/ml) for prolonged periods of time, recovery of virus is straightforward. Infants are considered to have a congenital infection if virus is recovered within the first 2 weeks of life. Infections during delivery in some cases can result in virus excretion within 2-3 weeks of age, thus providing an opportunity to misclassify perinatally infected infants as congenital infections. Rapid diagnostic methods, including the use of monoclonal antibodies for detection of immediate-early gene proteins encoded

by the virus, allow diagnosis of CMV infections within 24 hrs of specimen collection and have been adapted to large scale screening of infants for congenital CMV infections.

The development of PCR has revolutionized the detection of many different microbial agents, including CMV. Perhaps the two most important applications of PCR in the diagnosis of congenital CMV infections has been the application of real time quantitative PCR and the potential value of PCR for large scale screening utilizing templates extracted from blood spot screening cards. Real time PCR analysis of viral DNA in blood and urine has been utilized to classify congenitally infected infants according to viral burden. These studies have suggested that it may be possible to identify infants at risk for the development of long sequelae very early in life based on measurement of the amount of viral DNA present in blood or urine (7). Because less than 15% of congenitally infected infants will develop long term sequelae, early identification of infants at risk could result in substantial savings of resources required for extended clinical follow-up of these infants. PCR has also been utilized to detect viral DNA in blood spot specimens taken as part of routine newborn screening. Although the results of several studies suggest that this assay is currently too insensitive for routine use, improvements in DNA recovery and improved solid phase collection system make it likely that this approach can be readily implemented in the near future. Finally, PCR has been used to detect CMV DNA in amniotic fluid and initially, many investigators believed that detection and quantitation of CMV DNA in amniocentesis specimens could be used prognostically to identify infants with significant disease associated with an intrauterine infection. These claims remain controversial and because reliability of results from amniotic fluid testing is limited to samples obtained after 20-21 weeks of gestation; this approach appears to have little practical value.

Serological assays have been utilized in the past as part of the evaluation for TORCH infections. In general, serological assays are of little value in

the diagnosis of congenital or perinatal CMV infections because of the transplacental transfer of maternal antibodies to the fetus and the persistence of maternal antibodies in the infant. Recently, several groups have utilized maternal IgM anti-CMV antibody levels coupled with IgG anti-CMV antibody avidity to estimate the timing of maternal infections (32, 42). These assays have been useful for counseling of women with CMV IgG antibody reactivity detected during routine prenatal screening programs as to potential risks of fetal infection with CMV.

Treatment

Human cytomegalovirus infections in allograft recipients and AIDS patients have been treated with several antiviral agents. The nucleoside analogs, ganciclovir, foscarnet, and cidofovir all inhibit CMV DNA replication and have sufficiently favorable pharmacological properties to justify their use in severe organ and life threatening infections. All have significant toxicity and that can limit both dose and duration of treatment in some patients. The results of a trial comparing the outcome of treatment with ganciclovir to historical observations in infants with congenital CMV infections suggested that 6 weeks of therapy can possibly improve long term hearing outcome (29). Although these findings were suggestive of a beneficial effect of ganciclovir treatment in infants with symptomatic infections, several aspects of the study limited definitive interpretation of the results. Additional studies are underway to further define the value of ganciclovir therapy in infants with congenital CMV infection.

Prevention

Several strategies have been proposed to limit congenital and perinatal CMV infections. Because almost all community acquired CMV infections are asymptomatic, it is difficult to identify individuals who are excreting CMV and thus are potentially infectious. Thus, strategies to limit spread of CMV to susceptible individuals have been only marginally successful, except in the

case of caretakers of small children who have been provided an extended program on the contribution of hygiene and transmission of CMV. Vaccines for the prevention of congenital CMV infection have been proposed since the late 1970's. Early vaccines were so-called attenuated replicating virus that was prepared by repeated in-vitro passage. Because there are as yet well defined virulence markers for CMV, it is impossible to define attenuation by any means other than testing in human volunteers. One candidate vaccine, the attenuated Towne vaccine, has been tested in a reasonably large number of volunteers. The Towne vaccine has been shown to reduce clinical symptoms in transplant recipients with CMV infection based on a clinical scoring system. The vaccine failed to prevent infection and in challenge studies carried out in seronegative volunteers, the Towne vaccine failed to limit symptomatic infection when volunteers were challenged with limited amount of virus (36). Subsequent studies have also shown that the Towne vaccine failed to limit virus acquisition in women exposed to young children excreting CMV (3). It was argued that the limited protection offered by the Towne vaccine could be explained by its limited replication in-vivo, i.e. it was too attenuated. More recently, chimeric vaccines have been engineered by using the Towne virus and a clinical viral isolate, Toledo. These viruses were designed to overcome the limited replication of Towne virus in-vivo but also to limit the virulence of the clinical isolate, Toledo. This vaccine has been tested in a small number of volunteers and its value in the prevention of congenital CMV infections remains undetermined.

A second vaccine strategy utilizes an adjuvanted recombinant form of a major envelop CMV glycoprotein, gB. Animal studies have suggested that a gB vaccine could induce a protective antibody response and several studies have suggested that anti-gB antibodies represent a major component of the virus-neutralizing response in human convalescent serum (15). The human gB vaccine has been shown to induce virus-neutralizing antibodies and an in-vitro CD4⁺ T lymphocyte response in volunteers. The

duration of the virus-neutralizing antibody response induced by the CMV gB antigen has been shown to be limited, a finding that could restrict its value as a vaccine. Clinical trials are currently underway to test the immunogenicity of this vaccine.

Although many investigators have argued that congenital CMV infection is a vaccine preventable infection, natural history studies have demonstrated that reinfection by a second strain of CMV are common in women with pre-existing CMV immunity (12). In addition, reinfection in some women can lead to clinically apparent congenital CMV infections in their offspring (9, 12). In fact, re-examination of several early natural history studies of congenital CMV infections suggest that a vaccine that induced a response equivalent to the level of immunity that follows natural infection would reduce the number of infants with congenital CMV infection by at most 50%. More importantly, this reduction would occur only in maternal populations with a significant number of women susceptible to primary infection in pregnancy. In maternal populations with high CMV seroprevalence, the vaccine would have a negligible impact and offer little efficacy in such populations. In summary, current vaccine strategies for prevention of congenital CMV infections are controversial. Whether congenital CMV infection is a vaccine preventable or modifiable disease in some populations remains unknown. Furthermore, it is unclear if CMV immunity that is similar to the immunity induced following natural infection can be generated by anything other than a replicating vaccine. However, the unknown long term consequences of CMV infection, particularly the postulated role of CMV in vascular disease, have lessened the enthusiasm for live CMV vaccines.

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Sažetak

PERINATALNA INFEKCIJA HERPESVIRUSIMA

W. J. Britt

Perinatalne virusne infekcije su i dalje glavni uzrok morbiditeta i mortaliteta novorođenčadi. Prisutnost infekcije kod majke s mnogim uzročnicima koji su poznati kao uzroci bolesti fetusa i/ili novorođenčeta nije povezana sa značajnim oboljenjem majke. Upravo spoznaja da imunitet majke može ograničiti transmisiju virusa i bolesti, predstavljala je čvrst temelj za razvoj cjepiva koji trebaju ograničiti pojavu perinatalnih infekcija. Cjepiva poput onoga protiv rubella virusa su gotovo eliminirali rubeolu kao bolest fetusa i/ili novorođenčeta. Herpesvirusi su također čest uzrok perinatalnih infekcija i mogu izazvati teška oboljenja. Infekcija s herpes simplex virusom za vrijeme neonatalnog perioda i do sada je predstavljala čest uzrok bolesti, a s povećanom incidencijom genitalnih herpesvirus infekcija i dalje će predstavljati značajan uzrok bolesti kod novorođenčadi. Srećom, dostupna je učinkovita antivirusna terapija, iako zakašnjela dijagnoza infekcije i dalje predstavlja neriješeni problem u procesu liječenja. Iako prijašnji pokušaji cijepljenja žena cjepivom protiv herpes simplex virusa nisu bili uspješni, i dalje se testiraju nova cjepiva. Cytomegalovirus je najčešći uzročnik virusnih infekcija fetusa. Do 10% posto djece sa ovom infekcijom može oboljeti i imati dugotrajne neurološke posljedice nakon intrauterine infekcije. Ranija istraživanja su upućivala da bi se kongenitalne infekcije mogle preventirati cijepljenjem. Pa ipak, novija istraživanja pokazuju da većina novorođenčadi inficirana in-utero nije bila zaštićena imunitetom majke. Prema tome, potrebno je preispitati ulogu imuniteta kod ovakvih infekcija u majke i djeteta. Antivirusna terapija u postnatalnom razdoblju je dala neke minimalne rezultate. Ako se slična terapija primjeni na inficirani fetus, to potencijalno može ograničiti oštećenje središnjeg živčanog sustava in-utero i razvoj dugotrajnih sekvela.

Deskriptori: PERINATALNA INFEKCIJA, HERPESVIRUS