Human cytomegalovirus (HCMV) infection is common in all populations with rates climbing as high as 60% to 70% in some cities in the United States (1). Of particular concern is the incidence of HCMV infection in pregnant women and neonates. Congenital infections can occur transplacentally while the baby is still in utero or perinatally when CMV is shed from the cervix in the late stages of pregnancy as well as in breast milk. Although intrauterine infection occurs less frequently than perinatal infection, it results in the most severe disease. In the United States, approximately 30,000 babies are born each year with congenital disease (2). They exhibit generalized Cytomegalic Inclusion Disease (CID) featuring petechiae, hepatosplenomegaly, jaundice, microcephaly, growth retardation (IUGR), prematurity, chorioretinitis, and central nervous system (CNS) diseases such as intracranial calcifications, ventriculomegaly, lissencephaly, pachygyria, dysmyelination, paraventricular cysts and calcifications. Up to 25% of neonates with CID die from disease complications, and more than 90% of survivors experience significant and permanent CNS and sensory impairments, including intellectual, motor, auditory and visual system deficits (3). Of the 5% to 10% of these infants transplacentally infected who are clinically asymptomatic at birth, 90% will go on later in life to experience sensorineural hearing loss (SNHL). In perinatal infections, the course is completely different and asymptomatic, though subtle effects on hearing and developmental abnormalities may begin to manifest during the preschool years.

The highest risk of intrauterine transmission occurs during primary, or first time, infection of the mother with fetal involvement in 35% to 40% of cases. Whereas, the risk of vertical transmission in moms previously infected with HCMV is only 1% to 3% (2). In such situations, the neonate is typically asymptomatic. The point of gestation when primary infection occurs has a large bearing on the outcome. Although primary infection at any stage of pregnancy presents a risk of vertical transmission, the greatest impact of infection is seen during the first trimester. Overall, the clinical manifestations of HCMV disease appears to directly correlate with the duration of infection in utero.

Gestational age also has a great effect on the rate of maternal shedding of HCMV. Studies have shown that this phenomenon increases overtime progressing from a cervical shedding rate of 0% to 2% in the first trimester, 6% to 10% in the second trimester, and 11% to 28% in the third trimester (1). As with all herpes family viruses, CMV is able to establish latency within its host by continuing to persist within the body after the resolution of primary infection. Like other members of the herpes family of viruses, the mechanisms underlying latency are poorly understood. Recent animal models of CMV infection have helped shed some light on host-virus interactions.

Human CMV Infection in Pregnant Women and Neonates

Human cytomegalovirus (HCMV) is a member of the herpes virus family which may cause significant morbidity and mortality in immunocompromised patients, including neonates. While HCMV infection of healthy adults may cause a mild mononucleosis, neonatal HCMV has been associated with congenital birth defects. No vaccine exists for HCMV but appropriate hygiene precautions can limit the spread of the virus to mothers and, subsequently, neonates.

Human cytomegalovirus (HCMV) is a member of Herpesviridae family of large enveloped DNA viruses (1). There are eight herpesviruses that are known to infect and cause morbidity and mortality in humans. The definitive characteristic of the herpesvirus family is the ability of these viruses to cause both acute lytic infections, as well as long term persistent latent infections. Thus, once an individual has been infected by HCMV, they remain infected with the virus for the remainder of their life. Throughout the course of an infected individual’s life, the virus may “reactivate” to generate productively replicating virus particles which may be spread to other, noninfected individuals. Since many HCMV infections are asymptomatic or “silent,” infected individuals may not know that they pose a risk for transmission to others. It is for this reason that asymptomatic HCMV infections in pregnant mothers poses a significant risk to fetuses and neonates.

Mechanisms of transmission

HCMV infections are found in all socioeconomic groups throughout all geographic locations in the world. It has been estimated by the United States Centers for Disease Control and Prevention (CDC) that between 50% and 80% of the adult population in the United States is seropositive for HCMV (2). While seroprevalence increases with age, the majority of these infections occur prior to puberty. In most cases, transmission of HCMV occurs person to person by close physical interaction which involves contact with secretion and excretion bodily fluids including saliva, blood, urine, tears, semen, vaginal fluid, and breast milk. Another source of HCMV transmission is receipt of solid organ or hematopoietic stem cell transplantation from an infected donor. HCMV is a member of the TORCHES group of pathogens that can cross the placenta so it is also spread by vertical transmission from mother to child.

HCMV infection in immunocompromised individuals

HCMV is a high risk pathogen for individuals who have an impaired adaptive immune response. Prior to the establishment of highly active anti-retroviral therapy (HAART), HCMV infections in human immunodeficiency virus (HIV) positive patients was a serious opportunistic infection. At that time, retinitis caused by HCMV was the primary cause of blindness in AIDS patients. HCMV remains the major pathogen of risk for solid organ transplant patients. More than half of all transplant cases exhibit evidence of HCMV infection. The associated morbidity of these infections is a major cause of rejection. For this reason, anti-HCMV drugs must be administered throughout solid organ transplants. While HCMV infection of solid organ transplant recipients are usually acute primary infections, CMV infection following stem cell transplants are frequently due to reactivation of latent virus.

HCMV pathogenesis in adults

Primary HCMV infection in an immunocompetent individual is usually subclinical, rarely causing illness. However, large scale infection can cause an HCMV infections mononucleosis that has a clinical presentation very similar to that caused by Epstein-Barr virus. HCMV “mono” may involve fever, myalgia, lymphadenopathy, splenomegaly, and hepatitis (3). Other, rare, symptoms of HCMV include tonsillitis, pneumonitis, myocarditis, arthritis, ulcerative colitis, and meningitis. Transplant patients may also present with retinitis, esophagitis, and gastritis. HCMV infection in transplant patients also predisposes them to infection with other opportunistic pathogens.

Of all the human herpes viruses described to date, cytomegalovirus (CMV) appears to cause the most fatalities. Although primary infections do not usually produce symptoms in healthy adults, several high-risk groups including immunocompromised individuals and the developing human fetus are at risk for life threatening CMV disease.
Human CMV Infection in Pregnant Women and Neonates

Continued from ...................... pg 1

HCMV infection during pregnancy

Most HCMV infections, including late-gestational in utero and neonatal, are subclinical. However, HCMV is the most common virus transmitted from infected pregnant mother to child. Approximately one-third of women with a primary HCMV infection during pregnancy, pass the virus on to the neonate (2). Thus, approximately, one in 150 children are born with congenital HCMV infections. Congenital HCMV infection is defined by detection of the virus in the newborns urine, blood, or saliva within three weeks of birth. Children with congenital HCMV present with small body size, jaundice, petechiae, hypotonia, and hepatosplenomegaly. They may also be prone to lethargy and seizures. Women who are planning to become pregnant may receive an HCMV blood test which detects the presence of immunoglobulin molecules directed against the virus. If the test is positive for HCMV, it is unlikely that the baby will be at risk for congenital HCMV. Seronegative mothers must take hygienic precautions.

Consequences of congenital HCMV in neonates

In the United States, between 1% and 4% of seronegative mothers get a primary HCMV infection during their pregnancy (2). If this infection results in HCMV transmission to the unborn child in utero during the first trimester, it may lead to birth defects. The most common consequence is HCMV chronic infection. In extreme cases, there may be central nervous system/perceptual defects or ocular/auditory damage. Approximately one in 750 children in the United States are born with or develop permanent disabilities due to HCMV. This translates into approximately 8,000 children a year. Permanent birth defects associated with congenital HCMV include, small head size, lack of coordination, mental disability, and lack of hearing and/ or vision. In extreme cases, congenital HCMV may result in death of the neonate.

HCMV and breastfeeding

HCMV may be transmitted through breast milk. Thus, breast feeding has an impact on HCMV epidemiology. The basis of this is the fact that the rate of HCMV reactivation in the mother coincides with the seroprevalance of HCMV in the mother (5). Considering this, the newborn population most at risk includes extremely immature (preterm) neonates. The current recommendation of the American Academy of Pediatrics (AAP) is for breast feeding of both term and preterm infants (4).

HCMV treatment and prevention

There is currently no vaccine available to prevent HCMV. Because the HCMV virus has evolved to possess an elaborate system of immune evasion strategies (6), current efforts to develop HCMV must focus on stimulating both the innate and adaptive immune system in order to be successful. The antiviral treatment of choice for HCMV is nucleoside analog ganciclovir (3) and it is given to all transplant patients. While ganciclovir may prevent hearing loss in children, it has been associated with serious side effects in some cases. Another nucleoside drug, cidofovir, is also available but is less prominent. Both of these drugs have been associated with the emergence to resistant viral strains. A new anti-HCMV drug, maribavir, is currently in clinical trials. The best way to prevent HCMV transmission is through behavior modification which emphasizes hygiene. Accordingly, women who are pregnant or who may become pregnant are recommended by the the Centers for Disease Control and Prevention (CDC) to take the following precautions (2).

- Wash hands often, especially after contact with saliva or diapers of young children.
- Never kiss children below the age of six years of age on the mouth or cheek.
- Do not share food, drinks, or utensils with young children.

Perspective

HCMV is a major human pathogen which places both the mother and child at risk. Importantly, HCMV is associated with congenital birth defects. Once infected, an individual remains infected for life and may spread the virus to others. Although effective antiviral drugs exist for HCMV, the problem is that most infections are asymptomatic. Existing research efforts are focusing on the development of an HCMV vaccine. Currently, the best way to prevent HCMV infection is to limit exposure to bodily fluids.

REFERENCES


Q: I received a faxed unsealed bag notification from your Specimen Resolution Center (SRC). What does this mean?

A: The purpose of this communication is to notify your office that a delivery was received by our facility from your office in an unsealed FedEx Labpack mailer. We notify you of this occurrence to draw your attention to the fact that items originally included may have been lost during transit by falling out of this open packet. Unless you include a specimen assay order with your request, this occurrence to draw your attention to the fact that items originally included may have been lost during transit by falling out of this open packet. Therefore, as a courtesy to our clients, we supply a general manifest or packing list of some kind detailing the names of the patient specimens intended for transport that the plastic seal be removed from the top of the adhesive. Then firmly press together both sides of the mailer from the center of the strip to the outside edges to be sure that a firm seal is consistently supplied.

If you have a question you would like addressed in future issues, please email your question(s) to QAQ&A@mdlab.com
1. True or False. CMV is the most common virus transmitted to a pregnant woman’s unborn child.

2. In which of the following body fluids can CMV be found?
   a) Urine  e) Tears  
   b) Saliva   f) Semen  
   c) Breast milk  g) Vaginal fluids  
   d) Blood  h) All of the above

3. Each year in the United States, about _______ children are born with congenital CMV infection.

4. True or False. Congenital CMV (meaning present at birth) is as common a cause of serious disability as Down syndrome, fetal alcohol syndrome, and neural tube defects.

Recent Publications

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Human semen quality and fecundity have been declining during the past decades due to environmental pollution and changes in lifestyle. Authors have undertaken this study to investigate the correlation between dietary preferences and semen quality in men. They have compared diets of normospermic and oligoasthenoteratospermic patients attending a reproductive assisted clinic. Dietary habits and food consumption along with semen parameters, hormone levels, Y microdeletions, and karyotypes have been analyzed. The study suggested that semen quality may be influenced by food intake. Men with poor semen quality had a more frequent intake of some food items like meat products or milk that may adversely affect semen quality or act as carriers of deleterious products to the reproductive system such as xenobiotics, mainly xenoestrogens or certain anabolic steroids. Other food items containing antioxidants and micronutrients were associated with a better semen quality. They were lettuce, tomatoes, and some fruits like apricots and peaches. Authors concluded that frequent intake of lipophilic foods like meat products or milk may negatively affect semen quality in humans, whereas some fruits or vegetables may maintain or improve semen quality.


A retrospective study was performed to assess the clinical predictive value of quantification of CMV DNA in amniotic fluid (AF) samples by Real-time PCR. This is of interest because the value of these results as a prognostic indicator is controversial; there are results both supporting and disproving that a high CMV load in AF is associated with risk of symptomatic infection in the fetus. Here, the results of the PCR for CMV in 282 previously collected AF samples were obtained. Clinical data (available for 35 of the 41 women positive for CMV in AF), such as the presence or absence of fetal symptoms and gestational age, were compared to the viral load determined by the PCR. The PCR showed high specificity, but negative results could not rule out congenital infection in the fetus, even when optimal sampling conditions are met. In addition, these studies could not determine a correlation between the CMV viral load in AF and the outcome for the fetus. Instead a relation between the viral load and the time in pregnancy when the amniocentesis was performed was observed which was not clinically relevant. It is proposed that other factors of the CMV infection, such as CMV or host genotype, may have a more influential role in fetal outcome.


To estimate the accuracy of the clinical diagnosis of the three most common causes of acute vulvovaginal symptoms (bacterial vaginosis, candidiasis vaginitis, and trichomoniasis vaginalis) using a traditional, standardized clinical diagnostic protocol compared with a DNA probe laboratory standard. This prospective clinical comparative study had a sample of 535 active-duty United States military women presenting with vulvovaginal symptoms. Clinical diagnoses were made by research staff using a standardized protocol of history, physical examination including pelvic examination, determination of vaginal pH, vaginal fluid amines test, and wet-prep microscopy. Vaginal fluid samples were obtained for DNA analysis. The research clinicians were blinded to the DNA results. The participants described a presenting symptom of abnormal discharge (50%), itching/irritation (33%), malodor (10%), burning (4%), or others such as vulvar pain and vaginal discomfort. According to laboratory standard, there were 225 cases (42%) of bacterial vaginosis, 76 cases (14%) of candidiasis vaginitis, 8 cases (1.5%) of trichomoniasis vaginalis, 87 cases of mixed infections (16%), and 139 negative cases (26%). For each single infection, the clinical diagnosis had a sensitivity and specificity of 80.8% and 70.0% for bacterial vaginosis, 83.8% and 84.8% for candidiasis vaginitis, and 84.6% and 99.6% for trichomoniasis vaginalis when compared with the DNA probe standard. Compared with a DNA probe standard, clinical diagnosis is 81-85% sensitive and 70-99% specific for bacterial vaginosis, Candida vaginitis, and trichomoniasis. Even under research conditions that provided clinicians with sufficient time and materials to conduct a thorough and standardized clinical evaluation, the diagnosis and, therefore, subsequent treatment of these common vaginal problems remains difficult.
defense mechanisms and its ability to control viral infection particularly the role of the cell-mediated immune response. Multiple genetically distinct strains of HCMV exist and differences in genotypes may be associated with differences in virulence. Infection with more than one strain of HCMV is possible and has been observed in organ transplant patients as well as in women who attended a sexually transmitted disease clinic (1). Thus, reinfection that can result in HCMV infection in a seropositive immune mother likely occurs from exposure to a HCMV strain previously unencountered by the immune mother.

Accurate and prompt diagnosis is essential for the prevention and monitoring of HCMV infections. The laboratory diagnosis of HCMV infection can be performed by virological, serological, cellular, and molecular techniques as outlined in Table 1. The combination of these methods enables the discrimination between primary and secondary infection, viral characterization, and the monitoring of viral shedding. HCMV can be isolated from urine, blood, cervical secretions, saliva, breast milk, and semen.

Table 1: Laboratory assays currently used for the detection and antibody response to HCMV. Adapted from reference 8.

<table>
<thead>
<tr>
<th>TEST</th>
<th>METHOD</th>
<th>ASSAY TIME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell Culture</td>
<td>Detection of CPE in fibroblast cell line</td>
<td>4 wks</td>
</tr>
<tr>
<td>DEAFF test</td>
<td>‘Shell vial’ assay using fibroblast cell line</td>
<td>24–48 h</td>
</tr>
<tr>
<td>Serological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG, IgM</td>
<td>EIA / ELISA / Western blot</td>
<td>3–5 h</td>
</tr>
<tr>
<td>Cellular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antigenaemia</td>
<td>Immunofluorescence to detect pp65 matrix protein of CMV</td>
<td>5 h</td>
</tr>
<tr>
<td>Molecular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nucleic acid amplification</td>
<td>PCR: qualitative or quantitative viral load</td>
<td>5 h</td>
</tr>
</tbody>
</table>

Virological methods of laboratory testing include cell culture. Human fibroblast cells, the only human cell able to support CMV replication in vitro, are used to visualize hallmark cytopathic effects (CPE) of the virus such as characteristic large round cells with “ground-glass” appearing inclusions in the cytoplasm. Although cell culture is considered the “gold standard” for the detection of CMV, the appearance of CPE can take anywhere from 2 to 21 days, with a mean time of 8 days (4). The use of shell vial techniques may be combined with the use of monoclonal antibodies for the detection of early antigen fluorescent foci (DEAFF) for the diagnosis of HCMV. This process bypasses the need for the presence of CPE which enables results to be available much sooner. Limitations of these assays include the fact that both primary and secondary or recurrent infection may result in positive findings. Also, asymptomatic individuals may shed very low levels of HCMV virus or none at all (5).

Serological detection methods include the detection of IgG and/or IgM via enzyme immunoassay (EIA), enzyme linked immunosorbent assay (ELISA), and Western blot. For the best diagnostic results, it is suggested that paired specimens be obtained two weeks apart to detect differences in titer. These values are used in comparison to help distinguish between active and previous infection. Such interpretations are complicated by the fact that IgM levels can often become detectable during reactivation of latent infection (6). Limitations include the inability to use serological testing for the detection of congenital infection in newborns. Cross reactivity with other herpes family viruses, antinuclear antibody, or rheumatoid factor may produce false positives (5).

Cellular methods include an immunofluorescence based procedure where monoclonal antibodies are used to directly detect the presence of the HCMV pp65 phosphoprotein, which is the viral early matrix protein predominantly found in leukocytes during active HCMV infections. The major disadvantage of this test, when compared to other detection methods such as PCR, is timing for the detection of HCMV prior to the development of disease which is only 5 days as compared to 17 days for molecular methods such as PCR testing (4).

The advent of molecular methods, such as the polymerase chain reaction (PCR) method, enables clinicians to have a rapid and very sensitive technique for the detection of small amounts of HCMV DNA in many body fluids to enable early diagnosis (1). PCR testing has also proven to be a useful tool in the diagnosis of congenital HCMV infection through the detection of HCMV DNA in urine (7).

Despite the range of assays available, it is still not possible to accurately predict which fetuses will be infected and to what extent symptoms will manifest (8).

REFERENCES:
WorldWide Medical Products, Inc.

- Item Number - 14001003
  Small Vaginal Speculum, Indiv. Wrapped
  10/pack - $37.95

- Item Number - 14001004
  Medium Vaginal Speculum, Indiv. Wrapped
  10/pack - $39.95

- Item Number - 14001005
  Large Vaginal Speculum, Indiv. Wrapped
  10/pack - $41.95

- Item Number - 14011002
  Exam Table Rolls, Crepe, 21" x 125', White
  12/case - $24.92

- Item Number - 14011006
  Exam Table Rolls, Smooth, 21" x 125', White
  10/pack - $35.76

- Item Number - 31031000
  3" Cotton Tipped Applicator
  1000/box - $3.15

- Item Number - 31031001
  6" Cotton Tipped Applicator
  1000/box - $4.49

- Item Number - 31031005
  5½" Tongue Depressors Sterile
  1000/case - $32.95

- Item Number - 31031006
  6" Tongue Depressors Sterile
  1000/case - $32.95

- Item Number - 71011000
  Powder-Free Latex Gloves
  1000/case - $48.95

- Item Number - 71011005
  Powder-Free Nitrile Gloves
  1000/case - $54.95

- Item Number - 11021001
  MyLenis Bathroom Tissue
  80 rolls/case - $59.95

- Item Number - 11021000
  MyLenis Facial Tissue
  90 boxes/case - $54.95