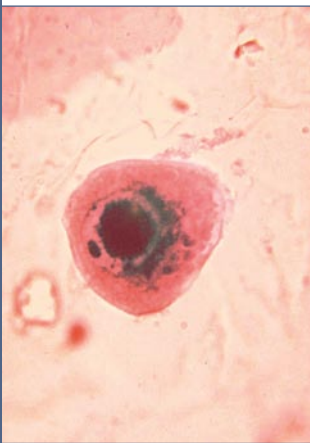


CMV Virus Overview

ABOUT THE VIRUS

Cytomegalovirus (CMV) is a linear, double-stranded DNA virus with an icosahedral capsid and is a member of the Herpesviridae family, which infects humans along with HSV-1, HSV-2, VZV, EBV, HHV-6, HHV-7 and HHV-8. CMV is also known as HHV-5. CMV, HHV-6 and HHV-7 are all members of the Betaherpesvirinae subfamily. The replication cycle of CMV is slow and produces large, multinucleated cells (cytomegalia). Once the virus has infected an individual, it establishes latency in lymphoreticular tissue, secretory glands, kidneys and other tissues. Human cytomegalovirus (HCMV) infects only humans and will grow in the laboratory only in cell lines of human origin.



Transmission electron micrograph of Cytomegalovirus infection of a cell in urine.
Courtesy of CDC/Dr. Haraszi.

CLINICAL MANIFESTATIONS

HCMV is ubiquitous throughout the world. When the virus is acquired at a young age it rarely causes any noticeable illness. However, in developed western countries, infection is often delayed, thus more likely to cause significant illness. The prevalence of antibodies among adults in the U.S. is between 40 and 100%, depending largely upon socioeconomic conditions. The infection rate gradually increases throughout childhood. Once infected, the individual carries the virus for the rest of their lifetime. It is estimated that at any given time up to 10% of the population is secreting CMV from various sources, such as urine, saliva, semen and breast milk. The virus is transmitted easily through any of these sources. Children, as well as daycare workers, are at high risk for contracting CMV since it is shed frequently in urine. In adults, primary CMV infection is typically acquired through blood transfusions, contact with an infected cervix or semen, or transplanted organ tissues. In young adults and CMV seronegative recipients of CMV positive blood transfusions, a syndrome resembling mild EBV mononucleosis is not uncommon. The patient will often present with prolonged fever, splenomegaly, abnormal liver function and atypical lymphocytes. The positive heterophile antibody test does not occur in CMV mononucleosis as in EBV mononucleosis.

Currently, transplacental infection with CMV is the most common viral cause of prenatal damage to fetuses. Approximately 1% of fetuses are infected with CMV in-utero, however, the majority of maternal infections are reactivations and rarely cause congenital CMV syndrome. Though, primary infection during the first trimester of pregnancy puts the fetus at higher risk for congenital CMV syndrome. Primary infection carries a 30-40% risk of fetal infection with a 10-15% risk of clinical abnormalities. A smaller percentage of those infants will suffer severe CMV syndrome, which can include microcephaly, thrombocytopenia, hepatosplenomegaly, petechial hemorrhages, jaundice, encephalitis, mental retardation and hearing impairment. Neonates can also acquire the virus during passage through the birth canal or contact with infected saliva and breast milk.

The immunocompromised population, including transplant patients, HIV patients and cancer patients (though to a lesser extent), are those at highest risk for developing the significant disease syndromes caused by CMV, including interstitial pneumonia, gastrointestinal infection, CNS disease, hepatitis, retinitis and encephalitis.

CMV is the most common and most important infectious agent among transplant recipients, both solid organ and hematopoietic stem cell transplant (HSCT) patients. Reactivation can occur in any individual who is latently infected, however, no transplant patient is safe from CMV since they can also acquire the virus from the transplanted organ or the virus can be community acquired following transplantation. This is of particular concern in pediatric transplant patients. In transplant recipients, the factor which influences the degree of morbidity and mortality is the type and extent of immunosuppression. Morbidity and mortality from CMV is lowest among kidney transplant patients and highest among bone marrow transplant patients, since they are the most profoundly immunocompromised.

LABORATORY DIAGNOSIS

A diagnosis of CMV cannot be made on solely clinical grounds; laboratory confirmation is required. Culture has been the traditional method to diagnose CMV infection, however, culture has several significant limitations: CMV can take up to 6 weeks to grow, the virus is temperature labile and may die before it reaches the laboratory, culture is not quantitative so viral load cannot be tracked, but most significantly, the amount of virus needed to cause disease in a transplant patient is far less than the amount of virus needed to grow in culture.

Another popular diagnostic method is the CMV antigenemia assay. A major step forward from culture, antigenemia is more sensitive, semi-quantitative and the assay can be performed in one day. However, the blood specimen must be less than 6 hours old to be tested and the assay is quite labor intensive and technically demanding. In this assay, the patient's white cells are removed from the whole blood specimen and attached to a glass slide. The cells are then stained with CMV specific monoclonal antibodies that are conjugated to a fluorescent molecule. The laboratory scientist then visualizes the patient's white cells under a fluorescent microscope and looks for cells containing CMV inclusions, which indicate that CMV is replicating in that cell. While this method is generally acceptable, there are several notable limitations. First, if the patient has a very low cell count, the specimen could be rejected. Secondly, there are reports in the literature of organ specific CMV disease occurring while the CMV antigenemia assay remains negative. This could be due to a mutation of the virus leading to a false negative result on the antigenemia assay. Alternatively, the CMV could be replicating only in the involved organ and not in the circulating white blood cells.

The need for a rapid, sensitive, specific and quantitative CMV detection system that overcomes the limitations of previous platforms has been acute. The advent of quantitative real-time PCR has dramatically improved CMV detection, thereby positively impacting transplant patient survival. Quantitative real-time PCR can be used to monitor the patient's response to antiviral drug treatment. Of further advantage, it can be performed on a wide variety of specimen sources including blood, CSF, urine, bronchial washes, eye swabs, tissue biopsies, and bone marrow biopsies, among others. Of note, it is important to choose the appropriate blood compartment for testing. Due to the highly sensitive nature of molecular testing, utilizing a cell based assay can yield positive results due to latent CMV in white blood cells. To avoid latent CMV, plasma can be used for testing, which will yield positive results only if actively replicating virus is present. A cell based CMV molecular assay can also encounter the same issues mentioned above in the CMV antigenemia discussion.

If CMV is replicating in white blood cells or a specific organ, there will be free virus circulating in the bloodstream, which can easily be detected when plasma is tested. For these reasons, ViraCor routinely utilizes plasma for testing of blood specimens.

TREATMENT

Treatment of a chronic viral infection, such as CMV, in an immunocompromised patient presents a special challenge. Antiviral medications may have limited effectiveness in these patients, or may stop suppressing replication of the virus once they are discontinued. Resistance to these agents is also an issue. Transplant programs typically take one of two approaches in an attempt to prevent and treat CMV disease: prophylactic treatment regimens or pre-emptive treatment regimens. In institutions that treat pre-emptively, an in-house protocol is usually followed as to when treatment with ganciclovir will be initiated, which is generally based on the results of a molecular based detection method or CMV antigenemia testing. Foscarnet is generally used in patients resistant to ganciclovir, because it is not as well tolerated.

Selected References

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