Introduction

Background

Cytomegalovirus (CMV) is a double-stranded DNA virus and is a member of the Herpesviridae family. The other family members include herpes simplex virus type 1 (HSV-1 or HHV-1) and herpes simplex virus type 2 (HSV-2 or HHV-2), varicella zoster virus (VZV), human herpesvirus (HHV)-6, HHV-7, and HHV-8. CMV shares many attributes with other herpes viruses, including genome, virion structure, and the ability to cause latent and persistent infections. CMV has the largest genome of the herpes viruses. Replication may be categorized into immediate early, delayed early, and late gene expression based on time of synthesis after infection. The DNA is replicated by rolling circles. Human CMV grows only in human cells and replicates best in human fibroblasts.

At least 60% of the US population has been exposed to CMV,[1] with a prevalence of more than 90% in high-risk groups (eg, male homosexuals).[2,3] The prevailing age of infection varies worldwide. In developing countries, most infections are acquired during childhood, whereas, in developed countries, up to 50% of young adults are CMV seronegative.

CMV usually causes an asymptomatic infection; afterward, it remains latent throughout life and may reactivate. Infection is defined as isolation of CMV, its viral proteins, or its nucleic acid from any tissue sample or body fluid.[4] In immunocompetent individuals, symptomatic disease usually manifests as a mononucleosis syndrome, which was first described in adults in 1965.[5]

Clinically significant CMV disease (reactivation of previously latent infection or newly acquired infection) frequently develops in patients immunocompromised by HIV infection, solid-organ transplantation, or bone marrow transplantation, as well as in those receiving high-dose steroids, tumor necrosis antagonists, or other immunosuppressing medications for conditions such as systemic lupus erythematosus (SLE), rheumatoid arthritis, Crohn disease, or psoriasis, among others. In patients coinfected with HIV, CMV infection leads to progression to AIDS and eventually death, even in those receiving highly active antiretroviral therapy (HAART).[6]

Symptomatic CMV disease in immunocompromised individuals can affect almost every organ of the body, resulting in fever of unknown origin, pneumonia, hepatitis, encephalitis, myelitis, colitis, uveitis, retinitis, and neuropathy.

Individuals at an increased risk for CMV infection include individuals who attend or work at daycare centers, patients who undergo blood transfusions, persons who have multiple sex partners, and recipients of CMV mismatched organ or bone marrow transplants.

CMV is transmitted from person to person via close contact with an individual who is excreting the virus. It can be spread through the placenta, blood transfusions, organ transplantation, and breast milk. It can also be spread through sexual transmission.

In the United States, congenital CMV transmission from a mother with acute infection during pregnancy is a significant
cause of neurological abnormalities and deafness in approximately 8000 newborns annually.\cite{7,8}

Multiple genetically distinct strains of CMV exist. Differences in genotypes may be associated with differences in virulence. Infection with more than one strain of CMV is possible and has been observed in organ transplant recipients. Dual infection is a possible explanation for congenital CMV infection in children of CMV-seropositive mothers.

**Pathophysiology**

CMV is a lytic virus that causes a cytopathic effect in vitro and in vivo. The pathologic hallmark of CMV infection is an enlarged cell with viral inclusion bodies. Cells that exhibit cytomegaly are also seen in infections caused by other Betaherpesvirinae. The microscopic description given to these cells is most commonly an "owl's eye," depicted in the image below. Although considered diagnostic, such histological findings may be minimal or absent in infected organs.

![Hematoxylin-eosin–stained lung section showing typical owl-eye inclusions (480X).](Image)

When the host is infected, CMV DNA can be detected with polymerase chain reaction (PCR) in all the different cell lineages and organ systems in the body. Upon initial infection, CMV infects the epithelial cells of the salivary gland, resulting in a persistent infection and viral shedding. Infection of the genitourinary system leads to clinically inconsequential viruria. Despite ongoing viral replication in the kidney, renal dysfunction is rare except in renal transplant recipients, in whom CMV is associated with rare cases of glomerulopathy and possible graft rejection.

**Immunology**
Primary CMV infection is defined as infection in an individual who was previously CMV seronegative.\[^4\] In these patients, CMV immunoglobulin M (IgM) antibodies may be found as early as 4-7 weeks after initial infection and may persist as long as 16-20 weeks. Most neutralizing antibodies are directed against an envelope glycoprotein gB. Studies have shown that more than 50% of neutralizing activity in convalescent serum is attributable to glycoprotein gB. However, virion tegument proteins such as pp150, pp28, and pp65 evoke strong and durable antibody responses.

CMV is an immunomodulatory virus and may aggravate underlying immune disorders (eg, SLE).

Cell-mediated immunity is considered the most important factor in controlling CMV infection. Patients deficient in cell-mediated immunity are at greatest risk for CMV disease. CMV-specific CD4\(^+\) and CD8\(^+\) lymphocytes play an important role in immune protection after primary infection or reactivation of latent disease. Studies of bone marrow transplant recipients have revealed that those who do not develop CMV-specific CD4\(^+\) or CD8\(^+\) cells are at higher risk for CMV pneumonitis. Additionally, no cases of CMV pneumonia have been reported in allogeneic marrow transplant recipients receiving infusions of CMV-specific CD8\(^+\) cells.\[^9\]

**Primary cytomegalovirus infection and viremia**

In most hosts, primary CMV infection is clinically silent. The presentation of symptomatic primary infection is addressed in Adult Cytomegalovirus Infection in the Immunocompetent Host. Primary CMV infection of the immunocompromised host carries the greatest risk for CMV disease.

Viremia is diagnosed by isolation of CMV in culture (either via standard or shell vial culture; see Laboratory studies).\[^4\] CMV excretion in the saliva and urine is common in immunocompromised patients and is generally of little consequence. In contrast, viremia in organ transplant recipients identifies those at greatest risk for CMV disease. The sensitivity of CMV viremia as a marker for CMV pneumonia is 60%-70% in allogeneic marrow transplant recipients. Having no evidence of virus in the bloodstream has a high negative predictive value for CMV disease. Prophylactic or preemptive antiviral therapy against CMV disease in transplant recipients typically relies on the detection of CMV in the blood by shell vial cultures, CMV antigenemia, and PCR amplification.

**Congenital cytomegalovirus disease**

Congenital CMV infection is one of the TORCH infections (toxoplasmosis, other infections including syphilis, rubella, CMV, and HSV), which carry a risk of significant symptomatic disease and developmental defects in newborns. The clinical syndrome of congenital cytomegalic inclusion disease includes jaundice, splenomegaly, thrombocytopenia, intrauterine growth retardation, microcephaly, and retinitis.

The most common clinical findings of congenital CMV infection include petechiae (71%), jaundice (67%), microcephaly (53%), and small size for gestational age (50%). Common laboratory abnormalities include hyperbilirubinemia (81%), increased levels of hepatocellular enzymes (83%), thrombocytopenia (77%), and increased CSF protein levels (77%). Studies have shown that asymptomatic children with neurological findings are more likely to have CMV IgM antibody. Many cases of hearing loss in children may be caused by CMV infection. CMV excretion is common in children with congenital infection and may represent a reservoir for infection in other children and daycare workers.

The CMV immune status of the woman is important in determining the risk of placental infection and subsequent symptomatic disease in the child or fetus. Symptomatic CMV congenital disease is less likely to occur in women with pre-existing immune responses to CMV than in CMV-naïve individuals. One in ten cases of acute CMV infection during pregnancy is estimated to result in congenital CMV disease.

**Cytomegalovirus pneumonia**

CMV pneumonia is defined as signs and symptoms of pulmonary disease in combination with detection of CMV in bronchoalveolar fluid or lung tissue.\[^4\] CMV detection should be performed via culture, histopathology,
immunohistochemical analysis, or in situ hybridization, as CMV DNA PCR testing alone is too sensitive for diagnosing CMV pneumonia.\[4 \]

Approximately 0%-6% of adults who present with CMV infection as a mononucleosis syndrome develop pneumonia. One study found that the incidence of CMV pneumonia in immunocompetent patients was 19%. In most cases, CMV pneumonia is found on chest radiography and is of no clinical significance, rapidly resolving with the disappearance of the primary infection.

Life-threatening CMV pneumonia may develop in immunocompromised patients (see Adult Cytomegalovirus Infection in the Immunocompromised Host). The highest rate of CMV pneumonia, as well as the greatest severity, occurs among lung transplant recipients, who are at an overall 50% risk of developing CMV illness (infection or disease).

Cytomegalovirus hepatitis

CMV hepatitis is defined as elevated bilirubin and/or liver enzymes levels in combination with the detection of CMV in the absence of other causes for hepatitis.\[4 \] CMV may be detected via culture, histopathology, immunohistochemistry, or in situ hybridization. CMV PCR alone is not satisfactory for diagnosis, as a positive result may reflect transient viral shedding.\[4 \] The first described case of CMV hepatitis involved a child with chorioretinitis, hepatosplenomegaly, and cerebral calcifications.

Hepatitis has been commonly observed in patients with primary CMV infection and mononucleosis. Levels of hepatocellular enzymes may be mildly and transiently increased, and, in rare cases, jaundice may develop. The prognosis of CMV hepatitis in immunocompetent hosts is typically favorable, but death has been reported in immunosuppressed patients. Histology typically reveals mononuclear cell infiltration of the portal areas but may also reveal granulomatous inflammation.\[10 \]

Cytomegalovirus gastritis and colitis

CMV GI disease is defined as the combination of symptoms of the upper and lower GI tract, mucosal lesions visible on endoscopy, and detection of CMV via culture, histopathology, immunohistochemistry, or in situ hybridization.\[4 \] CMV colitis was first described in 1985 in two homosexual men who presented with abdominal pain, diarrhea, and hematochezia.\[11 \] CMV PCR alone is insufficient for diagnosis, as a positive result may simply reflect transient viral shedding.

CMV may infect the GI tract from the oral cavity through the colon. The typical manifestation of disease is ulcerative lesions. In the oral cavity, these may be indistinguishable from ulcers caused by HSV or aphthous ulceration. Gastritis may present as abdominal pain and even hematemesis, whereas colitis more frequently presents as a diarrheal illness. CMV disease of the GI tract is often shorter-lived than that of other organ systems because of the frequent sloughing of infected cells of the GI mucosa.

Cytomegalovirus CNS disease

CMV CNS disease is defined as CNS symptoms in combination with CMV detection in CSF (culture, PCR) or brain biopsy tissue (culture, histopathology, immunohistochemistry, in situ hybridization).\[4 \]

Cytomegalovirus retinitis

CMV retinitis is one of the most common opportunistic infection in persons with AIDS, typically those with CD4\(^+\) lymphocyte counts below 50 cells/µL. Although the number of cases has decreased with the use of HAART, new cases continue to be reported. Individuals with CMV retinitis typically exhibit a progressive decrease in visual acuity, which may progress to blindness if untreated. Unilateral and bilateral disease may exist. Long-term CMV treatment is necessary to prevent retinitis relapse. All lesions suspected to be CMV retinitis must be confirmed by an
Immune reconstitution syndrome (IRIS) is reported in 16%-63% of HIV-infected patients with CMV retinitis following the initiation of HAART. In one study, the median time to IRIS following HAART initiation was 43 weeks but has been reported as early as 4 weeks or as late as 4 years in some cases. CMV IRIS may manifest as painless floaters, blurred vision, photopia, decreased visual acuity, or ocular pain. Some patients may develop macular edema leading to vision loss or proliferative vitreoretinopathy, spontaneous vitreal hemorrhage, and retinal detachment.

**Cytomegalovirus nephritis**

CMV nephritis is defined as CMV detection in combination with a renal biopsy showing CMV-associated changes in the setting of renal failure. CMV PCR alone is inadequate for diagnosis. Of note, detection of CMV in the urine of a patient with renal failure does not meet diagnostic criteria for CMV nephritis. CMV viremia has been associated with acute glomerular injury.

**Cytomegalovirus syndrome**

In general, it is better to avoid this term in stem cell transplant recipients, as other viruses (eg, HHV-6) can also cause fever and bone marrow suppression. However, in solid organ transplant recipients, CMV syndrome is better defined: fever (>38°C) for at least 2 days within a 4-day period, CMV detection in blood, and either neutropenia or thrombocytopenia.

**Graft versus host disease**

CMV infection has been associated with acute graft versus host disease in bone marrow transplant recipients. Multiple genotypes (gB 1-4) of CMV exist, each with variations in the gene encoding envelope glycoprotein gB. The association of gB types with acute graft versus host disease and death related to myelosuppression has been examined. Taking into account disease type, donor-recipient HLA matching, donor CMV serostatus, and age, Torok-Storb et al (1997) found that gB3 and gB4 were linked to a higher degree of myelosuppression and death. Interestingly, no specific CMV genotypes were linked to worse outcome in solid organ transplant recipients, although mixed gB genotype infections were associated with higher viral loads and delayed viral clearance.

**Frequency**

**United States**

CMV infection is thought to be specific to humans. The age at presentation, clinical manifestations, and route of infection may vary from person to person, but very few people escape infection during their lifetime.

**International**

Serologic surveys conducted worldwide demonstrate CMV to be a ubiquitous infection of humans. Depending on the population surveyed, CMV may be found in 40%-100% of people, depending on socioeconomic conditions. Infection earlier in life is typical in developing countries, whereas up to 50% of young adults are seronegative in many developed nations.

**Mortality/Morbidity**

CMV is seldom associated with mortality in nonimmunocompromised hosts (<1%). Substantial morbidity may occur in patients with a mononucleosis syndrome, as described in Adult Cytomegalovirus Infection in the Immunocompetent Host.

In both solid organ and marrow transplant recipients, CMV causes substantial morbidity and mortality. For example, even with antiviral therapy, the mortality rate in allogeneic marrow transplant recipients with interstitial pneumonia varies...
from 15%-75%.

**Age**

CMV prevalence increases with age. Age has also been found to be a risk factor for CMV disease in certain transplant populations.

**Clinical**

**History**

History varies depending on whether the host is immunocompetent or immunocompromised.

**Adult Cytomegalovirus Infection in the Immunocompetent Host**

Cytomegalovirus (CMV) can cause a wide spectrum of infection in immunocompetent hosts. Sites most often involved include the lung (severe community-acquired viral pneumonia), liver (transaminitis), spleen (splenomegaly), GI tract (colitis), CNS (encephalitis), hematologic system (cytopenias), and multisystem involvement (fever of unknown origin). Uncommon sites of CMV infections in immunocompetent individuals include the kidneys, adrenals, salivary glands, pancreas, and esophagus.\[5\]

In most cases, primary CMV infection is asymptomatic or produces mild flulike symptoms. Symptoms, when apparent, develop 9-60 days after primary infection. The lymph nodes and spleen may be enlarged, so CMV infection should be included in the differential diagnoses of infections that produce lymphadenopathy. Extreme fatigue may persist after normalization of laboratory values.

CMV may produce a mononucleosis syndrome similar to that caused by Epstein-Barr virus (EBV), primary toxoplasmosis, or acute HIV seroconversion. Both CMV and EBV may result in atypical lymphocytes in the blood. Other pertinent test results include negative findings on heterophil antibody studies, mildly or moderately elevated levels of aspartate aminotransferases, and evidence of subclinical hemolysis.\[19\] Hepatitis and atypical lymphocytes usually disappear after 6 weeks. Despite its great sensitivity, the CMV IgM test is limited by a one-way cross-reaction of acute EBV infectious mononucleosis sera. False-positive reactions have resulted from the presence of rheumatoid factors.\[19\]

CMV infection should be suspected in patients with clinical mononucleosis or fever of unknown origin. Most cases have a paucity of physical examination findings. Some studies have shown that, as a group, patients infected with CMV have less hepatomegaly, splenomegaly, and pharyngitis than those infected with EBV. Patients with CMV mononucleosis may be older, have a longer duration of fever, and have less cervical lymphadenopathy. However, such clinical findings are inadequate to differentiate between the two viruses.

Transfusion of multiple blood units is a risk factor for CMV mononucleosis and has been implicated in postoperative fever or fever in patients following trauma. Traditionally, CMV antibody tests were performed using complement fixation and showed peak viral titers 4-7 weeks after infection. Multiple tests for CMV antibody are now available, some of which are sensitive enough to detect anti-CMV IgM antibody early in the course of the illness and during CMV reactivation. Reactivation of the virus is not uncommon, sometimes occurring with viremia and a positive IgM result in the presence of IgG antibody. This is usually observed during intercurrent infections or at times of patient stress. The clinical significance, time course, and natural history of reactivation in immunocompetent patients are not known for either virus.

In rare cases, CMV can cause community-acquired pneumonia in immunocompetent hosts\[15\] and should be considered a possible etiology (along with influenza [human, swine, avian] and adenovirus) in cases of severe viral community-acquired pneumonia.\[5\] Case reports describe prolonged fever, lack of cough or other respiratory symptoms, bilateral interstitial or patchy infiltrates on chest radiography, relative lymphopenia, atypical lymphocytes, and mild transaminitis.\[20\] Of note, some patients had negative CMV IgM findings initially but subsequently developed elevated...
levels of both IgM and IgG, with resolution of the infiltrates over 6 weeks. There are varying degrees of hypoxemia. The prognosis of CMV pneumonia in immunocompetent hosts, even severe cases, is usually good, rarely requires a full course of antiviral treatment, and usually resolves during CMV induction therapy.

Rarer manifestations of CMV infections in immunocompetent individuals include Guillain-Barré syndrome, meningoencephalitis, pericarditis, myocarditis, thrombocytopenia, and hemolytic anemia. Rubelliform or maculopapular rashes are observed with and without administration of ampicillin. GI ulceration may result from acute CMV infection in immunocompetent persons, although this finding is much more likely in immunocompromised individuals.

**Adult Cytomegalovirus Infection in the Immunocompromised Host**

CMV infection in transplant recipients may be primary or recurrent. Again, the former refers to CMV detection in an individual who was previously seronegative, while recurrent infection includes both reinfection and reactivation. Reinfecion refers to detection of a CMV strain different from the one that caused the patient's original infection. Reactivation is defined as infection by the same CMV strain as was previously involved.

CMV infection may cause direct or indirect effects. Direct effects include bone marrow suppression, pneumonia, myocarditis, GI disease, hepatitis, pancreatitis, nephritis, retinitis, and encephalitis, among others. The main indirect effects include acute and chronic graft rejection, accelerated atherosclerosis (heart transplants), secondary bacterial or fungal infections, EBV-associated posttransplant lymphoproliferative disease (PTLD), and decreased graft and patient survival.

CMV infection may affect the same organ systems in HIV-positive patients with low CD4 counts as those in organ transplant recipients. Retinitis has been the major reported CMV disease in patients with HIV infection, followed by CNS involvement.

Not surprisingly, CMV disease has been associated with decreased survival in transplant recipients. As an example, in a group of 187 lung transplant recipients in Sweden between 1990 and 2002, the 10-year survival rate was only 32% in patients with CMV disease, compared with 53% among those with asymptomatic CMV infection and 57% in those without CMV infection.

**Organ transplantation and cytomegalovirus**

CMV is an important pathogen isolated in organ transplant recipients, as primary CMV infection in an organ transplant recipient may be quite severe. CMV disease occurs with the highest frequency in donor-positive/recipient-negative transplant recipients. This relationship is true for all organ transplant recipients except those who receive bone marrow, in whom the highest incidence of CMV disease is in donor-negative/recipient-positive individuals. The reason for this is unknown but may be related to the level of immunosuppression observed in patients who have received marrow transplants compared with those who have received other transplants.

Patients who have received marrow transplants undergo ablative chemotherapy and/or radiation. A period of neutropenia and a loss of specific antigen reactivity follow. All transplant recipients have a period of decreased CMV-specific cell-mediated immunity. The next step is unknown; however, patients at greatest risk for CMV disease develop viremia. The role viremia plays in the pathophysiology of CMV disease is unknown.

Life-threatening CMV pneumonia may develop in immunocompromised patients, with the incidence varying based on the type of transplant received. Patients who receive marrow, lung, heart, heart-lung, liver, pancreas-kidney, and kidney transplants have different levels of immunosuppression. Those most at risk include bone-marrow transplant recipients and recipients of lung transplants. In patients who have received marrow transplants, CMV disease is most likely 30-60 days after transplant. Fatal CMV pneumonia is much less common in patients who have received solid organ transplants than in those who have received marrow transplants. Patients may initially present with an asymptomatic infiltrate on chest radiograph.
The most common clinical presentation of CMV pneumonia is fever and shortness of breath, accompanied by an interstitial infiltrate. The differential diagnoses of CMV pneumonia in immunocompromised patients include \textit{Pneumocystis pneumonia}, viral respiratory infections, pulmonary hemorrhage, drug toxicity, recurrent lymphoma, and other infections. CMV is frequently detected in the lungs of patients with HIV/AIDS but usually represents viral shedding and does not frequently cause clinically significant disease.

CMV pneumonia is difficult to treat, even with the antivirals now available. The mortality rate among bone marrow transplant recipients with CMV pneumonia was approximately 85% prior to the introduction of ganciclovir and CMV-specific immune globulin. The addition of these drugs has decreased the CMV pneumonia mortality rate to 15%-75%. The mortality rate of CMV pneumonia in marrow transplants that requires mechanical ventilation is high, despite treatment with ganciclovir and immune globulin. Poor clinical outcomes are also observed in patients who are also infected with community respiratory viruses (eg, parainfluenza, influenza, respiratory syncytial virus) and those who have received allogeneic marrow transplants. This suggests that the severity of CMV pneumonia is not exclusively secondary to viral characteristics.

The use of immune globulin is based on studies of marrow transplant recipients, which noted improved survival rates in those with CMV pneumonia who received combination therapy (ganciclovir plus immune globulin).\cite{25} This has not been studied in patients with CMV pneumonia who have received solid organ transplants. Some experts believe that the mechanism of CMV pneumonia in patients who have received solid organ transplants may differ from that in marrow transplant recipients, making the addition of immune globulin unnecessary in the former. CMV pneumonia in marrow transplant recipients does not appear to involve a simple and direct viral cytopathic effect on pneumocytes. The addition of CMV-specific immune globulin has not been shown to affect the mortality and morbidity of CMV infection of other organ systems.

Severe CMV disease is likely secondary to synergism between the virus and other factors, such as radiation, chemotherapy, conditioning regimens, a nonimmune inflammatory response, or other infections. The diagnosis of CMV pneumonia depends on recovering CMV from patients with a positive finding on chest radiograph and appropriate clinical signs. CMV may be isolated from the lung with bronchoalveolar lavage (BAL) or open lung biopsy.

In support of the diagnosis, CMV antigen or inclusions are found with histological examination. CMV isolated from clinical samples in the absence of clinical symptoms may represent viral colonization or subclinical replication. In many cases, the detection of subclinical replication in transplant recipients warrants antiviral suppressive therapy. In patients infected with HIV, antiviral therapy is often not required in the absence of clinical apparent disease.

Primary GI CMV disease in solid organ transplant recipients is difficult to treat and may relapse. The relapse rate was recently studied in solid organ transplant recipients following treatment for CMV infection at the Mayo clinic. The investigators found that extensive involvement of the GI tract was significantly associated with CMV relapse but that endoscopic resolution of GI disease did not necessarily translate into a reduced risk of CMV relapse.\cite{26}

\textbf{Human immunodeficiency virus disease and cytomegalovirus}

CMV is often isolated from patients who are co-infected with other bacterial, parasitic, and fungal pathogens. In fact, CMV may be found in the lungs of approximately 75\% of individuals infected by both HIV and \textit{Pneumocystis}.\cite{5} The of CMV infection in \textit{Pneumocystis} pneumonia is unclear, and treatment of the latter usually leads to resolution of the pneumonia and hypoxemia, meaning that CMV treatment is not typically warranted in most cases.

For unknown reasons, CMV pneumonia without a co-infecting pathogen is uncommon.

In patients with HIV infection, CMV involves the entire GI tract. In the upper GI tract, CMV has been isolated from esophageal ulcers, gastric ulcers, and duodenal ulcers. Patients with upper GI tract esophageal disease can present with painful dysphagia. Patients with CMV disease of the lower GI tract may present with diarrhea (colitis). CMV colitis
frequently affects only the right colon, necessitating full colonoscopy and multiple biopsies for accurate diagnosis.\[^{27}\] Diagnosis of CMV GI disease depends on a biopsy specimen demonstrating the typical CMV intranuclear inclusions.

Recovery of CMV in tissue culture may be helpful but is difficult to interpret because of CMV shedding. CMV may be isolated from many different sites and is not necessarily associated with disease, reinforcing the need for histopathologic examination.

Retinitis is the most common manifestation of CMV disease in patients who are HIV positive. It occurs most commonly in patients with CD4 counts below 50 cells/µL, with rates of up to 40% in this population. Affected patients report decreased visual acuity, floaters, and loss of visual fields on one side. In many cases, it progresses to bilateral involvement that may be accompanied by systemic CMV disease. Ophthalmologic examination shows yellow-white areas with perivascular exudates. Hemorrhage is present and is often referred to as having a "cottage cheese and ketchup" appearance. Lesions may appear at the periphery of the fundus, but they progress centrally.

Ganciclovir has been used to treat CMV retinitis. Unfortunately, it only slows the progression of the disease. Many clinicians switch to foscarnet after ganciclovir fails. Ganciclovir implants have emerged as an important therapy in the management of CMV retinitis. The optimal treatment consists of ganciclovir implants in the vitreous, accompanied by systemic ganciclovir therapy. Oral ganciclovir may be used for prophylaxis of CMV retinitis but should not be used for treatment. The incidence of CMV retinitis has dropped since the widespread use of highly active antiretroviral therapy. During reconstitution of the immune response in patients who are HIV positive and on antiviral therapy, retinitis may worsen for a period. If severe inflammation is present, corticosteroid treatment may be necessary.

In patients who are HIV positive, CMV may cause disease in the peripheral and central nervous system.\[^{28}\]

**Physical**

Most patients with CMV infection exhibit few clinical findings on physical examination.

- Primary CMV infection may be a cause of fever of unknown origin.
- Symptoms, when apparent, develop 9-60 days after primary infection.
- Pharyngitis may be present.
- Examination of the lungs may reveal fine crackles.
- The lymph nodes and spleen may be enlarged, so CMV should be included in the differential diagnoses of infections that produce lymphadenopathy.
- Many physicians believe that CMV mononucleosis is less associated with pharyngitis and cervical adenopathy than EBV infectious mononucleosis. A recent study in young children questioned the accuracy of this clinical pearl. The study found that cervical adenopathy was more common in patients infected with EBV than in patients infected with CMV (83% versus 75%). Although statistically significant, relying on this sign for the differentiation between CMV and EBV mononucleosis is difficult.

**Causes**

See Adult Cytomegalovirus Infection in the Immunocompetent Host and Adult Cytomegalovirus Infection in the Immunocompromised Host.

**Differential Diagnoses**

| Autoimmune Hepatitis | HIV Disease |

http://emedicine.medscape.com/article/215702-print
Cytomegalovirus (CMV) has been detected via culture (human fibroblast), serologies, antigen assays, PCR, and cytopathology. The IgM level is elevated in patients with recent CMV infection, or there is a 4-fold increase in IgG titers. False-positive CMV IgM results may be seen in patients with EBV or HHV-6 infections, as well as in patients with increased rheumatoid factor levels.\[^5\]

Some tests are sensitive enough to detect anti-CMV IgM antibody early in the course of the illness (CMV early [nuclear] antigen, CMV viral capsid antigen) and during CMV reactivation. As with EBV infection, observing reactivation of the virus with a positive IgM result in the presence of IgG antibody is not uncommon. This is most commonly observed during intercurrent infection in immunocompromised patients.

An anti-CMV immediate early antigen monoclonal antibody test is now available.\[^29\]\ This reacts with an early protein and can detect CMV infection 3 hours into the infection. Intense coarse granular intranuclear inclusion staining is noted. No other nuclear staining or cytoplasmic staining is visualized.\[^29\]\

In the transplant population, antigen assays or PCR is used (sometimes in conjunction with cytopathology) for diagnosis and treatment determinations, with the choice of test varying among institutions.

**Antigen testing**

- Antigenemia is defined as the detection of the CMV pp65 antigen in leukocytes.\[^4\]\
- The pp65 assay is used to detect messenger matrix proteins on the CMV virus, with either immunofluorescence assay or messenger RNA amplification. These proteins are typically expressed only during viral replication.
- Antigen tests are often the basis for institution of antiviral therapy in transplant recipients and may allow for the detection of subclinical disease in high-risk patients. The assay is sensitive and specific yields results quickly.
- Antigen assays cannot be used in patients with leukopenia, as these tests detect antigen within neutrophils.
- In immunocompromised patients, low or moderate CMV antigenemia may indicate reactivation or infection.\[^5\]\
- It has been reported that the pp65 antigen assay and quantitative CMV PCR (COBAS Amplicor Monitor Test; see Quantitative polymerase chain reaction) yield similar effectiveness in diagnosing and monitoring patients with active CMV infection.\[^30\]\

**Qualitative polymerase chain reaction**

- Qualitative PCR is used to detect CMV in blood and tissue samples.
- PCR depends on the multiplication of primers specific for a portion of a CMV gene. The primers usually bind to the area of virus that codes for early antigen.
- Qualitative PCR is extremely sensitive, but, because CMV DNA can be detected in patients with or without active disease, the clinical utility of qualitative PCR is limited.\[^31,32,33\]\ Serial PCR may be more helpful clinically.
It yields a positive result before the antigenemia test in transplant recipients with viremia.

Results are typically negative in patients without CMV viremia.

In transplant recipients, a negative CMV PCR result goes against reactivation, but not infection.\[^{29}\]

**Quantitative polymerase chain reaction**

Quantitative PCR has been used to detect plasma CMV. The advantage of quantitative PCR over regular PCR is unknown. Ideally, quantitative PCR is as sensitive as qualitative PCR and provides an estimate of the number of CMV genomes present in plasma.

A study of more than 3400 blood specimens from organ transplant recipients tested with CMV PCR and pp65 antigenemia found that quantitative real-time PCR for CMV DNA could be used in lieu of antigenemia for monitoring CMV infection and determining when to initiate preemptive treatment.\[^{34}\]

In theory, the CMV viral load would indicate whether therapy is necessary because patients whose viral load is below a certain cutoff would not develop CMV disease. However, the level of viremia necessary for CMV disease to occur may vary depending on host factors and the type of organ transplant, and this may need to be determined empirically. For example, in CMV retinitis, the viral load has a poor positive predictive value, meaning its clinical utility is limited. A detectable CMV viral load at the time of CMV retinitis diagnosis was shown in one study to correlate with increased mortality (\(P = 0.007\)).\[^{35}\] CMV involvement of the GI tract also has a poor correlation with CMV viremia.

PCR assays include the COBAS Amplicor CMV Monitor test (research laboratories only) and the quantitative Hybrid Capture System CMV DNA test (neither of which is FDA approved), the qualitative Hybrid Capture test (FDA-approved), and institution laboratory–based PCR assays.\[^{36}\]

Because viral loads are not comparable among different assays, it is important to use the same test and same sample type (whole blood or plasma) when monitoring patients over time.\[^{37}\]

**Shell vial assay**

The shell vial assay is performed by adding the clinical specimen to a vial that contains a permissive cell line for CMV. The shell vials are centrifuged at a low speed and placed in an incubator. After 24 and 48 hours, the tissue culture medium is removed and the cells are stained using a fluorescein-labeled anti-CMV antibody. The cells are read using a fluorescent microscope. Alternatively, the cells are stained with an antibody against CMV, followed by a fluorescein-labeled anti–immune globulin.

This test has been found to be as sensitive as traditional tissue culture.

**Cytopathology**

Intracellular inclusions surrounded by a clear halo may be demonstrated with various stains (Giemsa, Wright, hematoxylin-eosin, Papanicolaou). This gives the appearance of an "owl's eye" (see Pathophysiology).
Hematoxylin–eosin–stained lung section showing typical owl-eye inclusions (480X). Courtesy of Danny L Wiedbrauk, PhD, Scientific Director, Virology & Molecular Biology, Warde Medical Laboratory, Ann Arbor, Michigan.

**Imaging Studies**

The diagnosis of CMV pneumonia can be suggested by chest radiography findings, but these findings cannot be used to differentiate between other common causes of pneumonia in immunocompromised hosts. A chest radiograph finding consistent with pneumonia and a BAL result that is CMV positive is a common method for diagnosis.

CT scan is more sensitive for the identification of infiltrate. It has been valuable in patients who present with hypoxia and no infiltrate visible on chest roentgenography.

**Other Tests**

**Cytomegalovirus resistance testing**

CMV infection continues to pose a major problem in transplant recipients, and antiviral resistance is encountered in all forms of transplantation. In solid-organ transplant recipients, ganciclovir resistance is found mainly among donor-positive, recipient-negative lung, kidney, and kidney/pancreas transplant recipients. Among stem cell transplant recipients, resistance primarily affects the donor-negative, recipient-positive group. Other risk factors include T-cell depletion, more than 3 months of antiviral therapy, very high viral loads, recurrent episodes of CMV disease, increased levels of immunosuppression, and suboptimal antiviral drug concentrations due to noncompliance or decreased absorption. Resistance to foscarnet and cidofovir has also been reported in solid-organ and stem cell transplant recipients.
Resistance typically takes weeks to months to develop. In fact, among patients with HIV infection, a 10% ganciclovir resistance rate has been reported at 3 months. Resistance should be suspected in patients who initially respond to CMV therapy but who subsequently develop an increasing viral load despite drug compliance. It should also be considered in patients who are clinically deteriorating.

Only two CMV resistance genes have been reported to date: UL-97 and UL-54. UL-97 (a phosphotransferase gene), encodes ganciclovir resistance, while UL-54 (viral DNA polymerase) mutations confer resistance to ganciclovir, foscarnet, and cidofovir. In approximately 90% of patients, ganciclovir resistance initially results from UL-97 mutations. To date, proven ganciclovir resistance mutations in UL-97 are found only in codons 460, 520, and 590-607. Mutations in codons 696-850 mediate foscarnet resistance, and mutations in these sites do not usually mediate cross-resistance to the other anti-CMV drugs. If a patient develops resistance while taking cidofovir, it is caused by a UL-54 mutation, which will encode cross-resistance to ganciclovir.

Specialized assays can be used to test resistance. The most widely used of these is a genotypic assay using fluid samples (eg, CSF, blood) that contain CMV DNA or samples with cultures positive for CMV. Genotype assay results can be performed and results received in a matter of days. Unfortunately, the assay is expensive and may pick up irrelevant mutations. Hence, familiarity in interpreting the results is key.

Other resistance assays include those used to measure viral load via antigenemia or quantitative DNA, as well as a phenotypic plaque reduction assay. The former is not well standardized, and interpretation may vary from one institution to the next. In addition, in certain CMV diseases (eg, retinitis), viral load testing yields a low positive predictive value. The plaque reduction assay takes at least 1 month to complete, is poorly standardized, and is not routinely performed in the laboratory.

**Histologic Findings**

The hallmark of CMV infection is the finding of intranuclear inclusions consistent with herpesvirus infection. CMV infection may be confirmed using in situ hybridization or direct or indirect staining of intranuclear inclusions using CMV-specific antibodies linked to an indicator system (eg, horseradish peroxidase, fluorescein).
Hematoxylin-eosin–stained lung section showing typical owl-eye inclusions (480X). Courtesy of Danny L Wiedbrauk, PhD, Scientific Director, Virology & Molecular Biology, Warde Medical Laboratory, Ann Arbor, Michigan.
Here, using immunofluorescent technique, a specimen of human embryonic lung (25X) reveals the presence of cytomegalovirus. Courtesy of the CDC/Dr. Craig Lyerla.

**Treatment**

**Medical Care**

The best options for treatment and prevention of cytomegalovirus (CMV) disease remain ganciclovir and valganciclovir. The other options listed below are either second-line (foscarnet or cidofovir) or are used off-label (leflunomide). There is no consensus at this time as to whether prophylaxis versus preemptive therapy is the better approach for prevention of CMV infection in solid-organ transplant recipients.

The incidence of CMV disease has significantly dropped in solid organ transplant recipients following the development of specific antiviral therapy.

For lifelong protection against CMV disease, the patient must develop a specific anti-CMV immune response.

**Ganciclovir treatment**

- The drug of choice for treatment of CMV disease is intravenous ganciclovir, although valganciclovir may be used for CMV treatment in selected cases.

- Ganciclovir is a nucleoside analogue that inhibits DNA synthesis in the same manner as acyclovir. The major
difference is that CMV does not contain a thymidine kinase.

- Protein UL97 phosphorylates ganciclovir to ganciclovir monophosphate. One of the mechanisms of ganciclovir resistance is a change in UL97. Mutations at codon 460 and 520 and mutations or deletions around codons 590-596 in UL97 cause most ganciclovir resistance, although other resistance mechanisms may be present.

- Ganciclovir has activity against CMV, HSV, VZV, and HHV-6, HHV-7, and HHV-8. However, one of the other nucleoside analogues (eg, famciclovir, penciclovir, acyclovir) is preferred to treat VZV and herpes simplex infections.

- The major adverse effects of ganciclovir therapy include fever, rash, diarrhea, and hematologic effects (ie, neutropenia, anemia, thrombocytopenia). Neutropenia is managed by dose reduction and/or the addition of growth factors (ie, granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF]).

- Oral ganciclovir results in serum levels that are 5-10 times less than intravenous ganciclovir, making oral ganciclovir a less-than-optimal agent for the management of active disease. Valganciclovir hydrochloride, an oral version (L-valyl ester) of ganciclovir, has been approved for the treatment of CMV retinitis in HIV-positive patients.

- A randomized trial of patients with CMV retinitis showed that oral valganciclovir was as effective as intravenous ganciclovir when used as an initial treatment. Although no trials have compared oral valganciclovir as a maintenance treatment, pharmacokinetic studies suggest valganciclovir is approximately as effective as intravenous ganciclovir.

- See the Medication section for dosing.

- In the treatment of CMV pneumonia, ganciclovir is administered with CMV-specific immune globulin (dosing in Medication section). However, it is unknown how immune globulin facilitates ganciclovir so that it leads to a better outcome in CMV pneumonia.

- The length of treatment varies. Some clinicians have administered ganciclovir for as long as 2-4 weeks from the end of the induction period, depending on the clinical status of the patient. Recently, investigators have studied shorter courses of intravenous ganciclovir therapy for CMV infection and disease, followed by transition to oral valganciclovir. If effective, this may help to improve patient quality of life and to reduce the length of hospital stay.

- Other uses of ganciclovir include treatment of GI disease in transplant recipients and in patients who are HIV positive. Ganciclovir has also been used to treat CMV esophagitis in both of these patient populations.

- The drug is also used to treat diarrhea secondary to colitis or enteritis in patients positive for HIV after tissue biopsy and confirmation of CMV disease. Because of the high probability of CMV disease relapse (50%), maintenance therapy should be offered to most patients.

- Ganciclovir has also been used to treat CNS disease, including encephalitis and neuropathy, with mixed results.

**Valganciclovir**

- Valganciclovir is a prodrug of ganciclovir that is activated in the gut and liver to ganciclovir.

- Valganciclovir has 60% bioavailability. Valganciclovir 900 mg orally once daily is equivalent to once-daily intravenous ganciclovir 5 mg/kg.

- Valganciclovir is used for treatment in selected CMV cases. Most experience has been established in renal
and pancreas transplant recipients and patients with AIDS who have CMV retinitis.

- It is also used for preemptive or universal CMV prophylaxis.
- A glomerular filtration rate (GFR) below 10 is a contraindication to valganciclovir use.

**Ganciclovir prophylaxis**

- A major successful use of ganciclovir has been prophylactic or preemptive treatment of CMV disease in transplant recipients. Without preventive CMV therapy, 30%-75% of transplant recipients develop CMV infection, and 8%-30% develop CMV disease.\[^{45,41}\]

- Oral ganciclovir has been replaced by valganciclovir for prophylaxis and preemptive therapy because of bioavailability issues.

- Prophylaxis is provided to all patients who have positive CMV serology results. Preemptive therapy is provided to patients who have evidence of ongoing viral replication. Positive findings on blood cultures, pp65 antigenemia, and CMV PCR have been used as markers for the initiation of therapy. Both the prophylactic and the preemptive approaches have been used, and both have been found to decrease CMV disease in bone marrow or solid organ transplants recipients. The choice of the appropriate regimen may be determined by the adverse effects of the drugs and the abilities of the microbiology laboratory. Universal prophylaxis versus preemptive therapy as the best approach remains a matter of debate and varies among institutions.

- Preemptive therapy is attractive because it restricts the use of ganciclovir to a select population at high risk for CMV disease, eliminates toxicity in most patients who would not be diagnosed with CMV disease, and decreases the cost of medical care.

- A study compared 96 renal transplant recipients in Italy between May 2006 and December 2007, all of whom received preemptive therapy with ganciclovir and/or valganciclovir, with 100 controls who received CMV prophylaxis. Serial quantitative viral loads were obtained weekly during the first 4 months. Asymptomatic patients, with a viral load DNA of more than 100,000 copies/mL determined using PCR, were treated with for 3 months or until resolution of viral replication. Among the 96 transplant recipients, blood CMV viral loads were elevated in 14 asymptomatic patients, who were treated with oral valganciclovir for 3 months. After a median follow-up period of 13.3 months, none of the 14 patients who received valganciclovir developed CMV disease, leading the authors to conclude that valganciclovir administered as preemptive therapy was safe and efficacious in preventing CMV disease.\[^{46}\]

- Conversely, a study using CMV pp65 antigenemia as the trigger for treatment found prophylaxis to be more effective than preemptive therapy for preventing CMV pneumonia in marrow transplant recipients.\[^{47}\] At the same time, however, ganciclovir at engraftment was associated with more early invasive fungal infections and more late CMV disease.\[^{47}\]

- Some experts believe CMV prophylaxis in solid organ transplant recipients may protect against indirect CMV effects not measurable by levels, such as graft rejection, opportunistic infections, and transplant-associated vasculopathy.\[^{41}\]

- Prophylactic approaches have also been very successful in eliminating CMV disease; however, toxicities are increased with this approach because patients without viral reactivation may be exposed to antiviral therapy. Many transplantation centers reserve prophylactic therapy for patients most at risk (CMV-positive donors/CMV-negative recipients) for disease reactivation and use antigen assays to institute preemptive therapy in other patients.

- Some experts recommend extending the duration of CMV prophylaxis to the period of reduced
immunosuppression. They feel this may protect patients from late-onset CMV disease.[41]

- Prolonged ganciclovir use has been associated with development of resistance.

**Foscarnet**

- Foscarnet is a DNA chain inhibitor of phosphorylation. It has been used to treat resistant HSV and ganciclovir-resistant viruses. It is an effective antiviral.
- Meticulous attention must be paid to the patient's renal function. Small changes in creatinine levels require new calculations for renal clearance. Foscarnet is nephrotoxic. The patient must be well hydrated.
- Foscarnet may cause changes in calcium and phosphorus metabolism. Other adverse effects include neurological toxicities, anemia, headache, and nausea. It can cause a fixed drug reaction on the penis.
- See the Medication section for dosing.
- Foscarnet does not require intracellular phosphorylation. Foscarnet resistance is secondary to mutations of the viral DNA polymerase involving codons from 696-845.

**Acyclovir prophylaxis**

- High-dose valacyclovir, penciclovir, famciclovir, and acyclovir have been used for CMV prophylaxis in organ transplant recipients. The results have been mixed and depend on the transplant population.
- European transplant groups are more likely to use acyclovir or valacyclovir for CMV prophylaxis than their US counterparts.
- In vitro assays have shown that some strains of CMV may be susceptible to acyclovir.
- Overall, acyclovir prophylaxis is not as effective as prophylaxis with ganciclovir.

**Cidofovir prophylaxis**

- Cidofovir is a nucleotide that inhibits DNA replication.
- It is effective against a broad range of viruses. It has been used for the treatment of refractory CMV retinitis in HIV-positive patients.
- Ganciclovir resistance does not necessarily preclude the use of cidofovir.
- See the Medication section for dosing.
- The patient must be hydrated, and the drug must be administered with probenecid to protect the renal tubules.

**Leflunomide**

- Leflunomide is an antimetabolite used as a disease-modifying agent in rheumatoid arthritis. It has also been successfully used off-label in both CMV disease treatment and prophylaxis.[48,49,50]
- Leflunomide failure has been reported in hematopoietic stem cell transplant recipients.[51]
- See the Medication section for dosing.
Cytomegalovirus immune globulin

- CMV immune globulin has been approved by the US Food and Drug Administration for the prophylaxis of CMV disease in high-risk lung transplant recipients when given in conjunction with ganciclovir. In a retrospective study of cardiothoracic transplant recipients, those who received CMV immune globulin plus ganciclovir had a higher disease-free incidence of CMV, less rejection, higher survival rate, and reduced coronary intimal thickening compared with patients who received ganciclovir alone.\(^{52}\) A prospective randomized study is required to confirm these observations.

- CMV immune globulin is used in combination with ganciclovir to treat CMV pneumonia.

- See the Medication section for dosing.

Consultations
Infectious diseases specialist

- Obtaining a consultation with an infectious disease specialist in patients with CMV viremia or pneumonia is prudent. This is particularly true in patients who are HIV positive, patients who have received organ transplants, and individuals who are immunocompromised in any other way (eg, heavy steroid use, tumor necrosis antagonists)

- Current antiviral medications have many adverse effects that are best managed by a physician who has experience using these drugs.

- Cidofovir and foscarnet have significant toxicity, including acute permanent renal failure. These drugs should be administered in conjunction with a clinician experienced in their usage.

Hematologist

- CMV infection may cause hemolytic anemia and thrombocytopenia.

- A hematologist may be consulted in severe cases.

Neurologist

- CMV may cause aseptic meningitis, encephalitis, polyneuritis, and Guillain-Barré syndrome.

- A neurologist may be helpful in the management of these diseases.

Ophthalmologist

- Chorioretinitis may be observed in immunocompromised hosts.

- In addition, consultation with an ophthalmologist is important in monitoring patients with HIV for opportunistic infections, especially patients with a CD4 cell count of fewer than 100 cells/µL.

Activity

Patients with CMV infection commonly ask when they can resume their usual activities. The most common symptom after resolution of the acute phase of CMV infection is fatigue, which may persist up to 18 months after the primary
infection but is usually much shorter. Some patients resume their usual activities almost immediately, but the average time to recovery from fatigue is 1-2 months. Patients should resume activity as they can tolerate.

Medication

The goals of pharmacotherapy are to prevent outbreaks of the disease and its complications and to reduce morbidity. Several agents are currently available for the treatment of cytomegalovirus (CMV) infection and disease.

In addition, multiple agents are in development for CMV treatment. These include (1) maribavir, an agent currently in a phase III randomized controlled trial with ganciclovir for CMV disease prevention in orthotopic liver transplant recipients; (2) CMX001 (hexadecyloxypropyl-cidofovir, an ester of cidofovir), which is under development as an oral treatment for smallpox; and (3) leflunomide, a pyrimidine synthesis inhibitor. Leflunomide has been successfully used in solid organ transplant recipients for both CMV treatment and prophylaxis. Unfortunately, leflunomide failure has been reported in hematopoietic stem cell transplant recipients.

Antivirals

CMV is a double-stranded DNA virus. Drugs currently used for the treatment of DNA viral infections affect the viral DNA polymerase and affect viral DNA replication.

Ganciclovir (Cytovene®)

Synthetic guanine derivative nucleoside analog active against CMV. Inhibits replication of herpes viruses both in vitro and in vivo.

In patients with HIV infection, resistance manifests as progressive disease. An oral formulation (valganciclovir) exists and is used for prophylaxis of CMV infection, but it should not be used for initial treatment of acute infection (except, perhaps, CMV retinitis). The oral version achieves serum levels comparable to those of the IV version.

Dosing

Adult

Adjust for renal impairment

CMV retinitis
Induction therapy: 5 mg/kg IV q12h for 14-21 days, followed by maintenance therapy
Maintenance: 5 mg/kg IV qd for 7 days/wk or 6 mg/kg for 5 days/wk
Oral: 1000 mg tid with food or 500 mg 6 times/day with food

Ocular implant: One implant intravitreally for 5-8 mo; following depletion of ganciclovir, as evidenced by progression of retinitis, implant may be removed and replaced

Prevention of CMV disease in patients with advanced HIV infection and normal renal function: 1000 mg PO 3 times/day with food

Prevention of CMV disease in transplant recipients: Same initial and maintenance dose as CMV retinitis except duration of initial course is 7-14 days; duration of maintenance therapy depends on clinical condition and degree of immunosuppression

CMV pneumonia
Induction: 5 mg/kg IV bid plus immune globulin 500 mg/kg 3 times/wk for the first 2 wks
Maintenance: 5 mg/kg IV for 1 mo plus immune globulin 500 mg/kg qwk for 1 mo
**Pediatric**

**Adjust for renal impairment**

Congenital CMV infection: 6 mg/kg IV q12h for 6 weeks in neonates and infants

CMV retinitis

<3 months: Not established

>3 months: Administer as in adults

Prevention of CMV disease in transplant recipients: 10 mg/kg IV divided q12h for 1-2 wk, followed by 5 mg/kg qd 7 days/wk or 6 mg/kg qd 5 days/wk for 100 days

Lung/heart-lung transplant recipients (CMV-positive donor with CMV-positive recipient): 6 mg/kg IV qd for 28 days

Other CMV infections

Initial: 10 mg/kg IV divided q12h for 14-21 days or 7.5 mg/kg divided q8h

Maintenance therapy: 5 mg/kg IV qd 7 days/wk or 6 mg/kg 5 days/wk

Oral (following induction treatment with IV ganciclovir): Maintenance dose, prophylaxis of CMV disease: 6 mo to 16 years: 30 mg/kg IV q8h with food

**Interactions**

Concomitant administration with dapsone, vinblastine, adriamycin, pentamidine, flucytosine, vincristine, amphotericin B, trimethoprim/sulfamethoxazole, or other nucleoside analogs may result in additive toxicity in bone marrow, spermatogonia, and germinal layers of skin and GI mucosa (coadminister only if potential benefits outweigh risks); coadministration with imipenem and cilastatin may cause generalized seizures (use only if potential benefits outweigh risks); serum creatinine may increase following concurrent use of ganciclovir with either cyclosporine or amphotericin B; renal clearance is reduced in the presence of probenecid; bioavailability may increase when didanosine is administered either 2 h prior to or simultaneously with ganciclovir; bioavailability may decrease in the presence of zidovudine, while the bioavailability of zidovudine is increased in the presence of ganciclovir

**Contraindications**

Documented hypersensitivity to ganciclovir, acyclovir, or any component; absolute neutrophil count <500/µL; platelet count <25,000/µL

**Precautions**

**Pregnancy**

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

**Precautions**

Toxicity includes granulocytopenia, anemia, and thrombocytopenia; dosages >6 mg/kg IV may result in increased toxicity; rapid infusions may result in increased toxicity; phlebitis or pain may occur at the site of IV infusion; administration should be accompanied by adequate hydration; photosensitization may occur

Monitor CBC count and electrolytes weekly (if stable on long-term therapy, frequency can be extended), serum creatinine, ophthalmologic status
Valganciclovir (Valcyte™)

L-valyl ester prodrug of ganciclovir.
Used for CMV disease prophylaxis in various solid organ transplant recipients. Inhibits replication of human CMV in vitro and in vivo.
Achieves serum levels comparable to those obtained with IV ganciclovir.

Dosing

**Adult**
CMV retinitis: 900 mg PO bid for 21 days, then daily; give with food
CMV disease induction dose: 900 mg PO q12h
CMV disease maintenance dose: 900 mg PO qd

CMV prophylaxis in heart, kidney, kidney-pancreas transplant recipients: 900 mg PO qd beginning within 10 days of transplant and continue for 100 days posttransplant

**Pediatric**
Valganciclovir solution preferred for children (aged 4 mo to 16 y), but pills may also be used
CMV prophylaxis for heart, kidney transplant recipients: 7 X BSA X CrCl, max; 900 mg PO qd; start within 10 days of transplant and continue for 100 days posttransplant

Interactions

Interactions are similar to those reported with ganciclovir; coadministration with cytotoxic drugs such as dapsone, vinblastine, doxorubicin, pentamidine, flucytosine, vincristine, amphotericin B, trimethoprim/sulfamethoxazole combinations, or other nucleoside analogs may result in additive toxicity of rapidly dividing cell populations, including bone marrow, spermatogonia, germinal layers of skin and GI mucosa; coadministration with imipenem-cilastatin may cause generalized seizures; serum creatinine levels may increase following concurrent use of ganciclovir with either cyclosporine or amphotericin B; in presence of probenecid, ganciclovir renal clearance is reduced; bioavailability may increase when didanosine is administered either 2 h prior to or simultaneously with ganciclovir; bioavailability of ganciclovir may decrease in presence of zidovudine; bioavailability of zidovudine is increased in presence of ganciclovir

May increase serum concentrations of ganciclovir
Ganciclovir-valganciclovir may increase serum concentrations of mycophenolate
Ganciclovir-valganciclovir may enhance the adverse/toxic effect of reverse transcriptase inhibitors (nucleoside); hematologic toxicity is of specific concern; ganciclovir-valganciclovir may decrease excretion of tenofovir

Coadministration with a high-fat meal increased AUC by 30%

Contraindications

Documented hypersensitivity to valganciclovir, ganciclovir, acyclovir, or any component of the formulation; severe renal dysfunction; pregnancy; breastfeeding women; absolute neutrophil count <500 cells/µL, platelet count <25,000/µL, hemoglobin <8 g/dL

Precautions

**Pregnancy**
C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus
Precautions

Valganciclovir tablets may not be substituted for ganciclovir capsules on one-to-one basis; adjust dose according to CrCl; may cause granulocytopenia, anemia, and thrombocytopenia

Not indicated for CMV disease prevention in liver transplant recipients (higher CMV disease incidence in liver transplantation compared to prophylaxis with ganciclovir)

Retinal examination (at least every 4-6 weeks), CBC count, platelet counts, serum creatinine

Foscarnet (Foscavir®)

Inhibits viral replication of herpesviruses (CMV, HSV-1, HSV-2) at pyrophosphate-binding site on virus-specific DNA polymerases. Used for ganciclovir-resistant CMV retinitis and herpes simplex disease.

Dosing

Adult

Adjust for renal impairment

CMV retinitis: Induction treatment: 60 mg/kg IV q8h for 14-21 days or 90 mg/kg IV q12h for 14-21 days

Maintenance therapy: 90-120 mg/kg as a single infusion once daily

Pediatric

Adjust for renal impairment

CMV retinitis: Induction treatment: 60 mg/kg IV q8h for 14-21 days

Maintenance therapy: 90-120 mg/kg as single infusion once daily

Interactions

Coadministration with potentially nephrotoxic drugs (eg, aminoglycosides, amphotericin B, IV pentamidine) may increase nephrotoxicity (do not administer unless potential benefits outweigh risks); coadministration with IV pentamidine may cause hypocalcemia

Contraindications

Documented hypersensitivity to foscarnet or any component

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

May cause decline in renal function; for correct dosing, obtain 24-h serum creatinine at baseline and continue to monitor (discontinue if serum creatinine <0.4 mL/min/kg); hydration may reduce nephrotoxicity; monitor electrolytes (eg, calcium, magnesium); granulocytopenia and anemia may occur (regularly monitor CBC count); to avoid toxicity, do not
administer by rapid or bolus IV injection; adverse effects include neurological toxicities, anemia, headache, and nausea; can cause a fixed drug reaction on the penis

Cidofovir (Vistide®)

Approved for treatment of CMV retinitis in AIDS. Nucleotide analog, whose active metabolite inhibits herpes virus polymerases at concentrations that are 8- to 600-fold lower than those needed to inhibit human cellular DNA polymerases alpha, beta, and gamma. Incorporation of cidofovir into the growing viral DNA chain results in reductions in the rate of viral DNA synthesis.

Dosing

Adult

Adjust for renal impairment

5 mg/kg IV q week times 2, then q2wk
Must be given with probenecid (2 g PO 3 h before each dose and additional 1 g PO doses 2 h and 8 h after cidofovir infusion completion)
Adequately prehydrate with normal saline

Pediatric

Adjust for renal impairment

Limited information in pediatric patients; some centers have used doses of 1 mg/kg 3 times/week or 5 mg/kg once weekly for 3 weeks, then every 2 weeks; oral probenecid 1.25 g/m²/dose is administered 3 h prior to and 1 h and 8 h after completion of each 1-hour cidofovir infusion; normal saline bolus equal to 3 times the maintenance fluid is administered for 1 h before cidofovir infusion and 1 h after, then decrease to 2 times the maintenance fluid for subsequent 2 h

Cytomegalovirus (CMV) retinitis

Induction: 5 mg/kg one time, with probenecid and hydration
Maintenance: 3 mg/kg once weekly, with probenecid and hydration

Interactions

Coadministration of aminoglycosides, amphotericin B, IV pentamidine, and foscarnet may increase nephrotoxicity

Contraindications

Documented hypersensitivity to cidofovir; history of clinically severe hypersensitivity to probenecid or other sulfas-containing medications; coadministration with other nephrotoxic agents; serum creatinine >1.5 mg/dL; CrCl<55 mL/min; proteinuria >100 mg/dL; use with or within 7 days of nephrotoxic agents; direct intraocular injection

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Monitor renal function (Cr, BUN, UA) within 48 hours of each dose; prehydrate with normal saline and coadminister
probenecid with each infusion to minimize nephrotoxicity; Administer LFT and WBC count (granulocytopenia may occur); monitor intraocular pressure and visual acuity, signs and symptoms of uveitis/iritis

**Antimetabolite**

These agents inhibit cell growth and proliferation.

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**Leflunomide (Arava®)**

Leflunomide has been used off-label in the treatment of cytomegalovirus (CMV) disease in transplant recipients, as well as in the prevention of acute and chronic rejection in recipients of solid organ transplants

Inhibits pyrimidine synthesis (via dihydroorotate dehydrogenase inhibition), leading to immunomodulatory and antiproliferative activity

**Dosing**

**Adult**

CMV (unlabeled use): 200 mg/d PO for 7 days, followed by 40-60 mg/d, versus "standard" RA dosing; adjust dose based on serum concentrations and adverse events

**Pediatric**

Not established

**Interactions**

Immunosuppressants may increase the hematologic toxicities of leflunomide (pancytopenia, agranulocytosis, and/or thrombocytopenia); may enhance adverse/toxic effect of leflunomide; concerns are an increased risk of pancytopenia and/or hepatotoxicity, including fatal; immunosuppressants may enhance adverse effects of natalizumab; may increase serum concentrations of active metabolite(s) of leflunomide; may enhance neutropenic effect of immunosuppressants; leflunomide may enhance anticoagulant effect of vitamin K antagonists; echinacea may diminish therapeutic effect of leflunomide

**Contraindications**

Documented hypersensitivity to leflunomide or any component of the formulation; pregnancy; concurrent live vaccines

**Precautions**

**Pregnancy**

X - Contraindicated; benefit does not outweigh risk

**Precautions**

CBC, serum phosphate, as well as serum transaminase determinations should be monitored at baseline and monthly during the initial 6 mo; if stable, monitoring frequency may be decreased to q6-8wk thereafter (continue monthly when used in combination with other immunosuppressive agents); monitor for signs/symptoms of severe infection, abnormalities in hepatic function tests, symptoms of hepatotoxicity, and blood pressure; obtain baseline PPD and pregnancy test; may cause Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme; can cause pancreatitis, interstitial pneumonitis, cholelithiasis

**Immune Globulin**

Consists of administration of immunoglobulin pooled from serum of immunized subjects.
Cytomegalovirus immune globulin (CytoGam®)

CMV immune globulin (CMV-IG) is a preparation of immunoglobulin derived from pooled healthy blood donors with high CMV titers; administration provides a passive source of antibodies against cytomegalovirus. Used for CMV pneumonia treatment. May also be used for CMV prophylaxis in heart, lung, kidney, liver and pancreas transplant recipients, in addition to ganciclovir.

Dosing

**Adult**

Severe CMV pneumonia: 400 mg/kg CMV-IG in combination with ganciclovir on days 1, 2, 7, followed by 200 mg/kg CMV-GIVE on days 14 and 21.

CMV prophylaxis in renal transplant recipients: 150 mg/kg IV X 1 within 72 h of transplant, followed by 100 mg/kg at weeks 2, 4, 6, 8, then 50 mg/kg at weeks 12, 16

CMV prophylaxis for recipients of other transplant (heart, lung, liver, pancreas): 150 mg/kg IV X 1 within 72 h of transplant, followed by 150 mg/kg at weeks 2, 4, 6, 8, then 100 mg/kg at weeks 12, 16

**Pediatric**

Severe CMV pneumonia: 400 mg/kg IV in combination with ganciclovir on days 1, 2, 7, followed by 200 mg/kg on days 14 and 21

**Interactions**

None reported

**Contraindications**

Hypersensitivity to CMV-IGIV, other immunoglobulins, or any component of the formulation; immunoglobulin A deficiency

**Precautions**

**Pregnancy**

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

**Precautions**

Monitor vital signs throughout infusion; watch for flushing, chills, muscle cramps, back pain, fever, nausea, vomiting, wheezing, anaphylaxis; monitor renal function and urine output; use with caution in patients >65 years; elderly patients may be at increased risk of renal insufficiency; aseptic meningitis has rarely been reported with IV immune globulin; hemolysis: immune globulin has been associated with hemolytic anemia; monitor for transfusion-related acute lung injury (TRALI) that may cause pulmonary edema; acute renal dysfunction can rarely occur; usually within 7 days of use; use with caution in elderly, patients with renal disease, diabetes mellitus, volume depletion, sepsis, paraproteinemia, and nephrotoxic medications; thrombotic events have been reported with administration of intravenous immune globulin

**Follow-up**

**Further Inpatient Care**
Patients with cytomegalovirus (CMV) disease must be well hydrated.

Nutrition is an important factor because many patients are debilitated by transplant or HIV disease.

As with any patient, attention must be focused on avoiding iatrogenic infections and problems.

Patients who develop CMV disease are immunocompromised, meaning that they are at greater risk for bacterial and fungal infections. If possible, the patient's level of immunosuppression should be lowered.

**Further Outpatient Care**

When ganciclovir is administered on an outpatient basis for the treatment of CMV retinitis, follow-up with a CBC count once per week (monitoring for hematological toxicity) is necessary. Monitoring electrolytes at the same time is prudent. Ganciclovir therapy should be stopped when neutrophil counts are less than 500 cells/µL. Starting growth factors, such as GM-CSF or G-CSF, may be necessary. A switch to foscarnet may be required at this time.

Patients with CMV retinitis should undergo regular ophthalmological examinations.

**Inpatient & Outpatient Medications**

See Medication section.

**Deterrence/Prevention**

See Treatment for a discussion about early treatment versus prophylaxis with ganciclovir.

- Other drugs have been used for CMV prophylaxis, but none is as effective as ganciclovir. Acyclovir and valacyclovir have been used for prophylaxis and early treatment in allogeneic marrow transplant recipients. Acyclovir has also been used in recipients of other types of transplants.

- CMV remains the most common viral cause of severe disease in the transplant population, with significant associated morbidity and mortality. This, together with the issue of drug treatment toxicities and drug interactions, makes the development of a successful vaccine a high priority. A bivalent DNA CMV vaccine, VCL-CB01 (which contains plasmids that encode CMV tegument pp65 and the major CMV surface glycoprotein B), was found to be well-tolerated in a phase 1 open-label study of 44 healthy adults and is now in phase II trials. These trials, which involve CMV-seropositive hematopoietic cell transplant recipients, have demonstrated that VCL-CB01 increases T-cell responses compared with placebo. The final results from this trial will be useful in developing strategies to prevent CMV disease in seropositive transplant recipients.

- Congenital CMV infection is an important cause of hearing, cognitive, and motor impairments in newborns. A phase II, placebo-controlled, randomized, double blind trial by Pass et al (2009) evaluated a recombinant CMV vaccine (envelope glycoprotein B with MF59 adjuvant). Three doses of the CMV vaccine or placebo were administered at 0, 1, and 6 months to 464 CMV-seronegative women within 1 year after they had given birth. After a minimum follow-up period of 1 year, 49 confirmed CMV infections were reported—18 in the vaccine group and 31 in the placebo group. One infant in the vaccine group was found to have congenital CMV infection, while 3 infants from the placebo group were infected. Ongoing research continues to evaluate the potential for a CMV vaccine to decrease maternal and congenital CMV infection.

**Complications**

See Medication.

Despite long treatment courses with valganciclovir and documented clearance of CMV viremia, CMV relapse remains common among solid organ transplant recipients. A better understanding of the epidemiology of CMV infection...
among solid organ transplant recipients and risk factors for disease relapse is warranted.

**Prognosis**

The prognosis of CMV hepatitis is generally good. Most patients recover completely. Symptoms can persist, usually in the form of fatigue, for several months after primary infection.

- CMV pneumonia in marrow transplant recipients once carried a mortality rate higher than 85%. The use of ganciclovir plus high-dose immune globulin for the treatment of CMV pneumonia in allogeneic marrow transplant recipients has lowered the mortality rate to 30%-60%.

- Because patients who develop CMV disease are immunocompromised, their prognosis may be determined by their underlying disease. The need for mechanical ventilation is a poor prognostic sign.

**Patient Education**

For excellent patient education resources, visit eMedicine's Bacterial and Viral Infections Center. Also, see eMedicine's patient education article Mononucleosis.

**Miscellaneous**

**Medicolegal Pitfalls**

Because of the toxicity of the antivirals used to treat cytomegalovirus (CMV) disease, consulting a physician familiar in the use and adverse effects of these drugs is important.

**Multimedia**
Media file 1: Here, using immunofluorescent technique, a specimen of human embryonic lung (25X) reveals the presence of cytomegalovirus. Courtesy of the CDC/Dr. Craig Lyerla.
Media file 2: Hematoxylin-eosin–stained lung section showing typical owl-eye inclusions (480X). Courtesy of Danny L Wiedbrauk, PhD, Scientific Director, Virology & Molecular Biology, Warde Medical Laboratory, Ann Arbor, Michigan.

References


51. [Medline].


36. Angela M Caliendo, MD, PhD. Viral load testing for cytomegalovirus in solid organ transplant recipients. Available


**Keywords**

cytomegalovirus, CMV, Betaherpesvirinae, Herpesviridae, mononucleosis, pneumonia, hepatitis, encephalitis, colitis, uveitis, retinitis, neuropathy, HIV, CMV syndrome, fever of unknown origin, FUO, STDs, transplant infections

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**Medical Editor**